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Appendix A: Details of literature search and study selection

Database searches in our broader systematic review[4] yielded 12,580 citations. A grey literature search identified 11 records, and reviewers nominated 25 records. We removed 488 duplicates and reviewed 12,128 bibliographic records at level 1 based on titles and abstracts. Of these, 10,911 were excluded and 1,217 records passed to level 2 for full-text screening. A further 1,180 records were excluded for not meeting the eligibility criteria and 37 articles (36 unique studies) were included[9–45] (PRISMA flow chart, Figure 1).

Search strategies of the broader systematic review

OVID

2018 Aug 7

Database: Embase Classic+Embase <1947 to 2018 August 06>, Ovid MEDLINE(R) ALL <1946 to August 06, 2018>

Search Strategy:

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1 Prosthesis-Related Infections/ (190992)
2 exp Joint Prosthesis/ae and (infect* or sepsis or septic*).tw,kw. (2674)
3 ((periprosthetic* or peri-prosthetic*) adj3 (infect* or sepsis or septic)).tw,kw. (3959)
4 (PJI or PJIs).tw,kw. (1948)
5 (((prosthe* or periprosthetic* or peri-prosthetic*) adj3 (joint$1 or knee$1 or hip or hips or shoulder$1 or wrist$1 or ankle$1 or elbow$1)) and (infect* or sepsis or septic)).tw,kw. (9874)
6 (((arthroplas* or replacement*) adj3 (joint$1 or knee$1 or hip or hips or shoulder$1 or wrist$1 or ankle$1 or elbow$1)) and (infect* or sepsis or septic)).tw,kw. (21507)
7 ((replacement* adj3 arthroplas*) and (infect* or sepsis or septic)).tw,kw. (416)
8 or/1-7 (212967)
9 Prosthesis-Related Infections/di [Diagnosis] (6684)
10 exp Sepsis/di [Diagnosis] (31123)
11 exp Arthritis, Infectious/di (8337)
12 Diagnosis/ (1508876)
13 Clinical Decision-Making/ (33752)
14 Delayed Diagnosis/ (14174)
15 Diagnosis, Differential/ (711821)
16 "Diagnostic Techniques and Procedures"/ (83402)
17 exp Clinical Laboratory Techniques/ (2593362)
18 Early Diagnosis/ (122374)
19 diagnos*.tw,kw. (5341486)
20 exp Biomarkers/an, bl (273977)
21 (biomarker* or marker?).tw,kw. (1957361)
22 Interleukin-6/an, bl (19656)
23 ((Interleukin-6 or "IFN-beta 2" or "IL-6" or IL6 or "MGI-2" or myeloid differentiation-inducing protein? or plasmacytoma growth factor? or B cell stimulatory factor? or B cell differentiation factor? or hepatocyte-stimulating factor? or hybridoma growth factor?) and (analys* or biomarker* or marker? or serum or blood or tissue?)).tw,kw. (183315)
24 Synovial Fluid/ (30259)

25 (((synovia* or synovium or articular or joint?) adj1 fluid?) and (analys* or biomarker* or marker? or serum or blood or tissue?)).tw,kw. (20264)
26 ((serum or blood or tissue?) adj3 (sampl* or screen* or test or tests or testing)).tw,kw. (739561)
27 or/9-26 (10716656)
28 8 and 27 (42599)
29 exp animals/ not (exp animals/ and humans/) (16087057)
30 28 not 29 (38080)
31 (comment or editorial or interview or news).pt. (1791395)
32 (letter not (letter and randomized controlled trial)).pt. (1957132)
33 30 not (31 or 32) (37258)
34 limit 33 to yr="2004-current" (12932)
35 (2016* or 2017* or 2018*).dt. (3151131)
36 34 and 35 (1090)
37 36 use medall [MEDLINE records] (1090)
38 periprosthetic joint infection/di (239)
39 periprosthetic joint infection/ (1115)
40 exp joint prosthesis/ and exp prosthesis infection/ (2233)
41 ((periprosthetic* or peri-prosthetic*) adj3 (infect* or sepsis or septic)).tw,kw. (3959)
42 (PJI or PJIs).tw,kw. (1948)
43 (((prosthe* or periprosthetic* or peri-prosthetic*) adj3 (joint$1 or knee$1 or hip or hips or shoulder$1 or wrist$1 or ankle$1 or elbow$1)) and (infect* or sepsis or septic)).tw,kw. (9874)
44 (((arthroplas* or replacement*) adj3 (joint$1 or knee$1 or hip or hips or shoulder$1 or wrist$1 or ankle$1 or elbow$1)) and (infect* or sepsis or septic)).tw,kw. (21507)
45 ((replacement* adj3 arthroplas*) and (infect* or sepsis or septic)).tw,kw. (416)
46 or/39-45 (27575)
47 exp prosthesis infection/di (1061)
48 exp Sepsis/di (31123)
49 exp infectious arthritis/di (8337)
50 diagnosis/ (1508876)
51 Clinical Decision-Making/ (33752)
52 Delayed Diagnosis/ (14174)
53 Diagnosis, Differential/ (711821)
54 "Diagnostic Techniques and Procedures"/ (83402)
55 exp Clinical Laboratory Techniques/ (2593362)
56 Early Diagnosis/ (122374)
57 diagnos*.tw,kw. (5341486)
58 (biomarker* or marker?).tw,kw. (1957361)
59 ((Interleukin-6 or "IFN-beta 2" or "IL-6" or IL6 or "MGI-2" or myeloid differentiation-inducing protein? or plasmacytoma growth factor? or B cell stimulatory factor? or B cell differentiation factor? or hepatocyte-stimulating factor? or hybridoma growth factor?) and (analys* or biomarker* or marker? or serum or blood or tissue?)).tw,kw. (183315)
60 (((synovia* or synovium or articular or joint?) adj1 fluid?) and (analys* or biomarker* or marker? or serum or blood or tissue?)).tw,kw. (20264)
61 ((serum or blood or tissue?) adj3 (sampl* or screen* or test or tests or testing)).tw,kw. (739561)
62 or/47-61 (10624356)
63 46 and 62 (7601)
64 38 or 63 (7601)
65 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (46306698)
66 exp humans/ or exp human experimentation/ or exp human experiment/ (36406260)
67 65 not 66 (9902138)
68 64 not 67 (7481)

69 editorial.pt. (997376)
70 letter.pt. not (letter.pt. and randomized controlled trial/) (1952456)
71 68 not (69 or 70) (7378)
72 limit 71 to yr="2004-current" (5483)
73 (2016* or 2017* or 2018*).dc. (3524148)
74 72 and 73 (785)
75 74 use emczd [EMBASE RECORDS] (785)
76 37 or 75 [BOTH DATABASES] (1875) [TOTAL UNIQUE RECORDS]
77 remove duplicates from 76 (1554)
78 77 use medall [MEDLINE UNIQUE RECORDS] (1087)
79 77 use emczd [EMBASE UNIQUE RECORDS] (467)

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Cochrane Library

Search Name: Periprosthetic Joint Infections - Update2 - Final
Date Run: 13/08/2018 14:43:16
Comment: 2018 Aug 8 - Updates Jan 2016 search

ID Search Hits
#1 MeSH descriptor: ["Prosthesis-Related Infections"] explode all trees 164
#2 [mh "Joint Prosthesis"/AE] and (infect* or sepsis or septic):ti,ab,kw 37
#3 ((periprosthetic* or (peri next prosthetic*)) near/3 (infect* or sepsis or septic)):ti,ab,kw 81
#4 (PJI or PJIs):ti,ab,kw 52
#5 (((prosthes* or periprosthetic* or (peri next prosthetic*)) near/3 (joint or joints or knee or knees or hip or hips or shoulder or shoulders or elbow or elbows or wrist or wrists or ankle or ankles)) and (infect* or sepsis or septic)):ti,ab,kw 447
#6 (((arthroplas* or replacement*) near/3 (joint or joints or knee or knees or hip or hips or shoulder or shoulders or elbow or elbows or wrist or wrists or ankle or ankles)) and (infect* or sepsis or septic)):ti,ab,kw 897
#7 ((replacement* near/3 arthroplas*) and (infect* or sepsis or septic)):ti,ab,kw 317
#8 {or #1-#7} 1088
#9 MeSH descriptor: ["Prosthesis-Related Infections"] explode all trees and with qualifier(s): [DI - DI] 27
#10 MeSH descriptor: [Sepsis] explode all trees and with qualifier(s): [DI - DI] 236
#11 MeSH descriptor: ["Arthritis, Infectious"] explode all trees and with qualifier(s): [DI - DI] 5
#12 MeSH descriptor: [Diagnosis] explode all trees 66
#13 MeSH descriptor: ["Clinical Decision-Making"] explode all trees 120
#14 MeSH descriptor: ["Delayed Diagnosis"] explode all trees 25
#15 MeSH descriptor: ["Diagnosis, Differential"] explode all trees 1443
#16 Any MeSH descriptor 28
#17 MeSH descriptor: ["Clinical Laboratory Techniques"] explode all trees 41637
#18 MeSH descriptor: ["Early Diagnosis"] explode all trees 1422
#19 diagnos*:ti,ab,kw 161906
#20 MeSH descriptor: [Biomarkers] explode all trees and with qualifier(s): [AN - AN, BL - BL] 12433
#21 (biomarker* or marker or markers):ti,ab,kw 55052
#22 MeSH descriptor: ["Interleukin-6"] explode all trees and with qualifier(s): [AN - AN, BL - BL] 2226
#23 ("Interleukin-6" or "IFN-beta 2" or "IL-6" or IL6 or "MGI-2" or ("myeloid differentiation-inducing" next protein*) or ("plasmacytoma growth" next factor*) or ("B cell stimulatory" next factor*) or ("B cell differentiation" next factor*) or ("hepatocyte-stimulating" next factor*) or ("hybridoma growth" next factor*)):ti,ab,kw 11212
#24 MeSH descriptor: ["Synovial Fluid"] explode all trees145

#25	((synovia* or synovium or articular or joint or joints) next (fluid or fluids)):ti,ab,kw	466
#26	{or #9-#25}	242338
#27	#8 and #26 with Cochrane Library publication date between Jan 2016 and Aug 2018	113

DSR - 1
DARE - 4
CENTRAL - 56

Appendix B: List of included studies with their characteristics

eTable A1: List of included studies with complete reporting of both sensitivity and specificity along their characteristics

First author (publication year)	Combination of tests (to call positive)	Cutoff	Logic / Type	Joint	Timing of index test	Total	PJI	No PJI	sens, spec as reported	PPV, NPV as reported	TP	TN	FP	FN	Risk of Bias
Chalmers (2014)[25]	Synovial WBC & PMN% positive	745 (WBC) & 73.5% (PMN%)	Type I	hips	pre- or intra-op	253	52	201	0.90 0.81	0.55 0.97	46.8	162.81	38.19	5.2	high
	Synovial WBC or PMN% positive	745 (WBC) or 73.5% (PMN%)	Type II	hips	pre- or intra-op	253	52	201	0.98 0.37	0.29 0.99	50.96	74.37	126.63	1.04	high
	Synovial WBC & PMN% positive	1700 (WBC) & 65% (PMN%)	Type I	hips	pre- or intra-op	253	52	201	0.88 0.82	0.56 0.97	45.76	164.82	36.18	6.24	high
	Synovial WBC or PMN% positive	1700 (WBC) or 65% (PMN%)	Type II	hips	pre- or intra-op	253	52	201	0.96 0.47	0.32 0.98	49.92	94.47	106.53	2.08	high
Cross (2014)[26]	Aspiration culture or Biopsy tissue culture positive		Type II	hips	pre-op	110	17	93	0.59 1.00	1.00 0.93	10	93	0	7	high
Glehr (2013)[12]	Serum CRP or Serum IL-6 positive	17.05 mg/L (CRP) or 4.7 pg/mL (IL-6)	Type II	mixed	pre-op	84	55	29	0.84 0.68	0.82 0.71	46.2	19.72*	9.28*	8.8	high
	Serum CRP or Procalcitonin positive	17.05 mg/L (CRP) or 0.75 ng/mL (PCT)	Type II	mixed	pre-op	84	55	29	0.83 0.83	0.89 0.74	45.65*	24.07	4.93	9.35*	high
	Serum CRP or Serum WBC positive	17.05 mg/L (CRP) or 7355/µL (WBC)	Type II	mixed	pre-op	84	55	29	0.93 0.59	0.81 0.81	51.15	17.11	11.89	3.85	high
	Serum IL-6 or Procalcitonin positive	4.7 pg/mL (IL-6) or 0.75 ng/mL (PCT)	Type II	mixed	pre-op	84	55	29	0.83 0.68	0.81 0.71	45.65*	19.72	9.28	9.35*	high
	Serum IL-6 or Serum WBC positive	4.7 pg/mL (IL-6) or 7355/µL (WBC)	Type II	mixed	pre-op	84	55	29	0.89 0.50	0.75 0.73	48.95	14.5*	14.5*	6.05	high
	Serum WBC or Procalcitonin positive	7355/µL (WBC) or 0.75 ng/mL (PCT)	Type II	mixed	pre-op	84	55	29	0.73 0.79	0.86 0.63	40.15	22.91	6.09	14.85	high
Janz (2013)[27]	Serum CRP or Histopathology of periprosthetic	Unknown (CRP) Morawietz and	Type II	mixed	pre-op (CRP)	59	23	36	0.96 0.72	0.96 0.69	22.08	25.92	10.08	0.92	high

	membrane positive	Krenn 2006 (Histopathology)			intra-op (PM)										
Fink (2013)[29]	Tissue culture or Histological analysis (>=5 PMNs/HPF) from biopsy	same organism identified in >=2 samples or >=5 PMNs/HPF in >=1 of 10 HPFs	Type II	hips	pre-op	100	45	55	0.82 0.98	0.97 0.87	37	54	1	8	unclear
	Aspiration culture or Biopsy (bacteriologic or histologic) positive	same organism identified in >=2 samples or >=5 PMN/HPF in >=1 of 10 HPFs	Unclear	hips	pre-op	100	45	55	0.87 0.98	0.98 0.90	39	54	1	6	unclear
	Serum CRP or Aspiration culture or Biopsy (bacteriologic or histologic) positive	CRP>10 mg/L or same organism identified in >=2 samples or >=5 PMN/HPF in >=1 of 10 HPFs	Unclear	hips	pre-op	100	45	55	0.84 0.87	0.84 0.87	38	48	7	7	unclear
Zmistowski (2012)[30]	Synovial WBC count divided by serum WBC count	>48%	Arithmetic	knees	pre-op	150	73	77	0.93 0.94	0.93 0.94	68	72	5	5	high
	Synovial PMN count divided by serum PMN count	>37%	Arithmetic	knees	pre-op	150	73	77	0.93 0.94	0.93 0.94	68	72	5	5	high
Johnson (2011)[33]	Serum CRP or Serum ESR positive	10 mg/L (CRP) or 30 mm/h (ESR)	Type II	knees	pre-op	113	105	8	0.95 0.38	NR	99.75	3.04	4.96	5.25	high
	Serum CRP & Serum ESR positive	10 mg/L (CRP) & 30 mm/h (ESR)	Type I	knees	pre-op	113	105	8	0.95 0.29	NR	99.75	2.32*	5.68*	5.25	high
Buttaro (2010)[9]	Serum CRP & Serum IL-6 positive	10 mg/L (CRP) & 10 pg/mL (IL-6)	Type I	hips	pre-op	69	11	58	0.57 1.00	1.00 0.94	6.27*	58	0	4.73*	high
Meermans (2010)[34]	Aspiration culture or Biopsy tissue culture positive	same organism grew on two or more specimens	Type II	mixed	pre-op	120	110	10	0.90 1.00	1.000 0.476	99	10	0	11	unclear
Schinsky (2008)[36]	Synovial WBC for patients with	>3000 WBC/mL given >10 mg/L	Conditional	hips	intra-op (WBC)	79	NR	NR	0.90 0.91	0.95 0.82	NR	NR	NR	NR	high

	elevated Serum CRP & ESR level	(CRP) & >30 mm/h (ESR)			pre-op (CRP, ESR)										
	Synovial WBC for patients with elevated Serum CRP & ESR level	>9000 WBC/mL given >10 mg/L (CRP) & >30 mm/h (ESR)	Conditional	hips	intra-op (WBC) pre-op (CRP, ESR)	79	NR	NR	0.81 0.90	0.94 0.77	NR	NR	NR	NR	high
	Synovial WBC for patients with elevated Serum CRP or ESR level	>3000 WBC/mL given >10 mg/L (CRP) or >30 mm/h (ESR)	Conditional	hips	intra-op (WBC) pre-op (CRP, ESR)	60	NR	NR	0.83 0.87	0.67 0.91	NR	NR	NR	NR	high
	Synovial WBC for patients with elevated Serum CRP or ESR level	>9000 WBC/mL given >10 mg/L (CRP) or >30 mm/h (ESR)	Conditional	hips	intra-op (WBC) pre-op (CRP, ESR)	60	NR	NR	0.83 1.00	1.00 0.98	NR	NR	NR	NR	high
	Synovial PMN% for patients with elevated Serum CRP & ESR level	>80% (PMN%) given >10 mg/L (CRP) & >30 mm/h (ESR)	Conditional	hips	intra-op (PMN%) pre-op (CRP, ESR)	79	NR	NR	0.87 0.90	0.93 0.82	NR	NR	NR	NR	high
Ghanem (2008)[37]	Serum CRP or Synovial WBC positive	10 mg/L (CRP) or 1100 WBC/μL (WBC)	Type II	knees	pre-op	429	161	268	0.992 0.415	0.561 0.986	159.71	111.22	156.78	1.29	high
	Serum ESR or Synovial WBC positive	30 mm/h (ESR) or 1100 WBC/μL (WBC)	Type II	knees	pre-op	429	161	268	0.987 0.591	0.632 0.985	158.91	158.39	109.61	2.09	high
	Serum CRP or Synovial PMN% positive	10 mg/L (CRP) or 64% (PMN%)	Type II	knees	pre-op	429	161	268	1.000 0.446	0.579 1.000	161	124.89	143.11	1	high
	Serum ESR or Synovial PMN% positive	30 mm/h (ESR) or 64% (PMN%)	Type II	knees	pre-op	429	161	268	0.967 0.664	0.674 0.966	155.69	177.95	90.05	5.31	high
	Synovial WBC or Synovial PMN% positive	1100 WBC/μL or 64% (PMN%)	Type II	knees	pre-op	429	161	268	0.975 0.833	0.780 0.982	156.98	223.24	44.76	4.03	high
	Serum CRP & Synovial WBC positive	10 mg/L (CRP) & 1100 WBC/μL	Type I	knees	pre-op	429	161	268	0.861 0.930	0.902 0.898	138.62	249.24	18.76	22.38	high
	Serum ESR & Synovial WBC positive	30 mm/h (ESR) & 1100 WBC/μL	Type I	knees	pre-op	429	161	268	0.850 0.967	0.949 0.900	136.85	259.16	8.84	24.15	high

	Serum CRP & Synovial PMN% positive	10 mg/L (CRP) & 64% (PMN%)	Type I	knees	pre-op	429	161	268	0.891 0.970	0.958 0.921	143.45	259.96	8.04	17.55	high
	Serum ESR & Synovial PMN% positive	30 mm/h (ESR) & 64% (PMN%)	Type I	knees	pre-op	429	161	268	0.888 0.981	0.971 0.924	142.97	262.91	5.09	18.03	high
	Synovial WBC & Synovial PMN% positive	1100 WBC/µL & 64% (PMN%)	Type I	knees	pre-op	429	161	268	0.850 0.992	0.986 0.916	136.85	265.86	2.14	24.15	high
Fink (2008)[38]	Tissue culture or Histological analysis (>=5 PMNs/HPF) from biopsy	same organism identified in >=2 samples or >=5 PMNs/HPF in >=1 of 10 HPFs	Type II	knees	pre-op	145	40	105	1.000 0.981	0.952 1.000	40	103	2	0	unclear
Austin (2008)[39]	Serum CRP or Serum ESR positive	10 mg/L (CRP) or 30 mm/h (ESR)	Type II	knees	pre-op	296	116	180	0.96 0.56	0.58 0.95	111	100.8	79.2	5	high
Bottner (2007)[11]	Serum CRP or Serum IL-6 positive	35 mg/L (CRP) or 12 pg/mL (IL-6)	Type II	mixed	pre-op	78	21	57	1.00 0.86	0.72 1.00	21	49.02	7.98	0	unclear
Deirmengian (2014)[40]	Usage of synovial CRP only if alpha-defensin was positive	Positive if alpha-defensin > 5.2 mg/L and CRP > 3 mg/L	Triage-Conditional	mixed	pre-op	149	37	112	0.973 1.000	1.000 0.991	36	112	0	1	high
Elgeidi (2014)[10]	Serum CRP & Serum IL-6 positive	18 mg/L (CRP) & 10.4 pg/mL (IL-6)	Type I	mixed	pre-op	40	11	29	1.00 0.99	0.92 1.00	11	28.71*	0.29*	0	high
Ettinger (2015)[41]	Usage of serum CRP only if serum IL-6 > 5.12 pg/mL	Positive if IL-6 > 5.12 pg/mL and CRP > 3 mg/L	Triage-Conditional	mixed	pre-op	98	41	57	0.750 0.982	0.938 0.918	30.75*	55.97	1.03	10.25*	high
Petti (2015)[43]	Tissue culture or PCR positive		Type II	mixed	intra-op	82	45	37	1.00 0.78	0.55 1.00	45	28.86	8.14	0	high
Wu (2014)[13]	Serum CRP positive or single site frozen section >=5 PMNs/HPF	15 mg/L (CRP) or histological analysis >=5 PMNs/HPF	Type II	mixed	pre-op (CRP) intra-op (histology)	156	37	119	0.92 0.79	0.59 0.99	34.04	94.01	24.99	2.96	high
	Serum CRP positive & single site frozen section >=5 PMNs/HPF	15 mg/L (CRP) & histological analysis >=5 PMNs/HPF	Type I	mixed	pre-op (CRP) intra-op (histology)	156	37	119	0.65 0.99	0.96 0.90	24.05	117.81	1.19	12.95	high

	Serum ESR positive or single site frozen section >=5 PMNs/HPF	30 mm/h (ESR) or histological analysis >=5 PMNs/HPF	Type II	mixed	pre-op (ESR) intra-op (histology)	156	37	119	0.92 0.65	0.40 0.96	34.04	77.35	41.65	2.96	high
	Serum ESR positive & single site frozen section >=5 PMNs/HPF	30 mm/h (ESR) & histological analysis >=5 PMNs/HPF	Type I	mixed	pre-op (ESR) intra-op (histology)	156	37	119	0.54 0.98	0.91 0.87	19.98	116.62	2.38	17.02	high
Ghanem (2009)[35]	Serum CRP or Serum ESR positive	10 mg/L (CRP) or 30 mm/h (ESR)	Type II	hips	pre-op	479	127	352	0.976 0.587	0.482 0.984	123.95	206.62	145.38	3.05	high
	Serum CRP or Serum ESR positive	20.5 mg/L (CRP) or 31 mm/h (ESR)	Type II	hips	pre-op	479	127	352	0.961 0.592	0.500 0.973	122.05	208.38	143.62	4.95	high
	Serum CRP & Serum ESR positive	10 mg/L (CRP) & 30 mm/h (ESR)	Type I	hips	pre-op	479	127	352	0.878 0.881	0.745 0.948	111.51	310.11	41.89	15.49	high
	Serum CRP & Serum ESR positive	20.5 mg/L (CRP) & 31 mm/h (ESR)	Type I	hips	pre-op	479	127	352	0.748 0.890	0.742 0.893	95	313.28	38.72	32	high
Gallo (2018)[14]	Serum IL-6 & Synovial CRP	12.55 ng/L (serum IL-6) & 8.8 mg/L (synovial CRP)	Type I	mixed	pre-op (serum IL-6), pre- or intra-op (synovial CRP)	59	19	40	0.737 1.000	1.000 0.889	14	40	0	5	high
	Serum IL-6 & Synovial IL-6	12.55 ng/L (serum IL-6) & 20,988 ng/L (synovial IL-6)	Type I	mixed	pre-op (serum IL-6), pre- or intra-op (synovial IL-6)	48	19	29	0.632 1.000 (based on counts)	1.000 0.806 (based on counts)	12	29	0	7	high
Balato (2018)[15]	Serum CRP & Serum ESR	10 mg/L (CRP) & 30 mm/h (ESR)	Type I	knees	pre-op	51	16	35	0.813 0.829	0.684 0.906	13	29	6	3	High
Ottink (2018)[16]	Synovial fluid culture or Tissue biopsy culture	same pathogen isolated from >= 2 separate tissue or fluid samples	Type II	hips	pre-op	29	11	18	0.82 1.00	1.00 0.90	9.02	18	0	1.98	high

Fink (2018)[17]	Serum CRP or Joint aspiration culture	10 mg/L (CRP); unclear for joint aspiration culture (possibly same pathogen in >=2 samples)	Unclear	knees	pre-op	116	27	89	0.778 0.955	0.840 0.934	21	85	4	6	unclear
	Serum CRP or Joint aspiration culture or PCR		Unclear	knees	pre-op	116	27	89	0.852 0.820	0.589 0.948	23	73	16	4	unclear
Wouthuyzen-Bakker (2018)[18]	Serum CRP & Serum ESR	10 mg/L (CRP) & 30 mm/h (ESR)	Type I	mixed	pre-op	31	11	20	0.637 0.750	0.583 0.800	7.007	15	5	3.993	high
Balato (2018)[19]	Serum CRP & Serum ESR	10 mg/L (CRP) & 30 mm/h (ESR)	Type I	knees	pre-op	167	31	136	0.806 0.890	0.625 0.952	25	121	15	6	high
Fernandez-Sampedro (2018)[20]	Peri-implant tissue culture or histopathology	Morawietz and Krenn 2006 (histopathology) or >=2 cultures yielded the same microorganism; only a single positive required when S. aureus or S. lugdunensis were the microorganisms isolated	Type II	mixed	intra-op	496	128	368	0.961 0.997	0.992 0.987	123	367	1	5	high
	Serum CRP or Synovial fluid culture	10 mg/L (CRP) or >=2 cultures yielded the same microorganism; only a single positive required when S. aureus or S. lugdunensis were the microorganisms isolated	Type II	mixed	pre-op	423	114	309	0.798 0.845	0.655 0.919	91	261	48	23	high

	Serum CRP or Peri-implant tissue culture	10 mg/L (CRP) or >=2 cultures yielded the same microorganism; only a single positive required when S. aureus or S. lugdunensis were the microorganisms isolated	Type II	mixed	pre-op (CRP) intra-op (tissue culture)	495	128	367	0.859 0.845	0.659 0.945	110	310	57	18	high
Berger (2017)[21]	Serum CRP & Serum ESR	10 mg/L (CRP) or 30 mm/h (ESR)	Type II	mixed	pre-op	77	20	57	0.750 0.772	0.536 0.898	15	44	13	5	high
Pohlig (2017)[22]	Synovial WBC or percentage neutrophils	unknown thresholds	Type II	hips	pre-op	10	5	5	0.80 0.60	0.667 0.750	4	3	2	1	high
	Preoperative tissue culture or histology (>=23 PMNs/10 HPFs)	same pathogen identified in >=2 cultures or >=23 PMNs/10 HPFs	Type II	hips	pre-op	20	8	12	0.875 1.000	1.000 0.920	7	12	0	1	high
	Serum CRP or Synovial WBC or percentage neutrophils	5 mg/L (CRP), unknown for synovial WBC, %neutrophils	Unclear	hips	pre-op	10	5	5	0.80 0.80	0.80 0.80	4	4	1	1	high
	Serum ESR or Synovial WBC or percentage neutrophils	30 mm/h (ESR), unknown for synovial WBC, %neutrophils	Unclear	hips	pre-op	7	4	3	0.75 1.00	1.00 0.75	3	3	0	1	high
	Serum CRP or serum ESR or synovial WBC or percentage neutrophils or aspiration culture	5 mg/L (CRP), 30 mm/h (ESR), unknown for synovial WBC, %neutrophils, same pathogen identified in >=2 cultures	Unclear	hips	pre-op	20	8	12	0.875 0.917	0.875 0.917	7	11	1	1	high
Sousa (2017)[23]	Synovial CRP or Synovial WBC	6.7 mg/L (CRP) or 1463/µL (WBC)	Type II	mixed	intra-op	55	23	32	1.000 0.656	0.676 1.000	23	20.992	11.008	0	high

	Synovial CRP or Synovial PMN%	6.7 mg/L (CRP) or 81% (PMN%)	Type II	mixed	intra-op	55	23	32	0.956 0.688	0.688 0.956	21.988	22.016	9.984	1.012	high
	Synovial CRP & Synovial WBC	6.7 mg/L (CRP) & 1463/µL (WBC)	Type I	mixed	intra-op	55	23	32	0.783 1.000	1.000 0.865	18.009	32	0	4.991	high
	Synovial CRP & Synovial PMN%	6.7 mg/L (CRP) & 81% (PMN%)	Type I	mixed	intra-op	55	23	32	0.609 1.000	1.000 0.780	14.007	32	0	8.993	high
	Synovial WBC & Synovial PMN%	1463/µL (WBC) & 81% (PMN%)	Type I	mixed	intra-op	55	23	32	0.783 0.750	0.692 0.828	18.009	24	8	4.991	high
Claassen (2016)[24]	Preoperative tissue culture or histopathology	Morawietz and Kenn 2006 (histopathology) or infecting specimen verified in at least two of five samples (culture)	Type II	knees	pre-op	34	8	26	0.88 0.88	0.70 0.96	7	23	3	1	high

Abbreviations: FP=false positive; FN=false negative; sens=sensitivity; spec=specificity; TP=true positive; TN=true negative; PPV=positive predictive value; NPV=negative predictive value.
Note: TP, TN, FP, FN were either reported (as counts) or calculated using the reported sensitivity and specificity (as non-integer in the table).
*: rounding of calculated TP/FN or TN/FP counts contradicted reported sensitivity or specificity at the 1% decimal place

eTable A2: List of included studies with incomplete reporting of sensitivity or specificity

First author (publication year)	Combination of tests (to call positive)	Cutoff	Logic / Type	Joint	Timing of index test	Total	Sens as reported	Spec as reported	PPV	NPV	AUC	Risk of Bias
Gollwitzer (2013)[28]	Predictive score of IL-6 & LL-37 (but only reported AUC)	Not reported for -3.392 + 0.040 x LL-37 + 0.374 x IL-4	Model-based	mixed	pre-op	35	NR	NR	NR	NR	0.895	high
	Predictive score of IL-4 & LL-37 (but only reported AUC)	Not reported for -3.287 + 0.921 x LL-37 -0.002 x IL-6	Model-based	mixed	pre-op	35	NR	NR	NR	NR	0.916	high
	Predictive score of IL-6 & HBD-3 (but only reported AUC)	Not reported for -2.072 - 0.005 x HBD-3 + 0.003 x IL-6	Model-based	mixed	pre-op	35	NR	NR	NR	NR	0.849	high
	Predictive score of IL-4 & HBD-3 (but only reported AUC)	Not reported for -7.025 - 0.020 x HBD-3 + 1.276 x IL-4	Model-based	mixed	pre-op	35	NR	NR	NR	NR	0.972	high
Toossi (2012)[31]	Serum WBC & neutrophil percentage (but only reported PPV)	7800 cells/µL (WBC) & 69% (neutrophil percentage)	Type I	mixed	pre-op	930	NR	NR	0.60	NR	NR	high

	Serum WBC or neutrophil percentage (but only reported NPV)	7800 cells/µL (WBC) or 69% (neutrophil percentage)	Type II	mixed	pre-op	930	NR	NR	NR	0.55	NR	high
Costa (2012)[32]	Serum CRP or Serum ESR (but only reported false negative rate)	10 mg/L (CRP) or 30 mm/h (ESR)	Type II	hips	pre-op	66	0.97	NR	NR	NR	NR	high
Friedrich (2014)[42]	Serum CRP & Serum LBP (but only reported PPV and NPV)	90 mg/L (CRP) & 7 ng/mL (LBP)	Type I	mixed	pre-op	120	NR	NR	0.67	0.77	NR	high
Spangehl (1999)[44]	Serum CRP & Serum ESR (but only reported PPV)	10 mg/L (CRP) & 30 mm/h (ESR)	Type I	hips	pre-op	142	NR	NR	0.83	NR	NR	high
	Serum CRP or Serum ESR (but only reported NPV)	10 mg/L (CRP) or 30 mm/h (ESR)	Type II	hips	pre-op	142	NR	NR	NR	1.00	NR	high
Randau (2014)[45]	Serum IL-6 & Synovial IL-6 (but only reported PPV and NPV)	2.6 pg/mL (serum IL-6) & 2100 pg/mL (synovial IL-6)	Type I	mixed	pre-op (serum IL-6), pre- or intra-op (synovial IL-6)	120	NR	NR	0.89	0.453	NR	high
	Serum IL-6 or Synovial IL-6 (but only reported PPV and NPV)	2.6 pg/mL (serum IL-6) ot 2100 pg/mL (synovial IL-6)	Type II	mixed		120	NR	NR	0.547	0.78	NR	high

Abbreviations: sens=sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value.

Appendix C: Additional table and figures

Additional Table

eTable A3: Reported diagnostic accuracy (specificity, sensitivity) of type I and type II Boolean combinations of synovial WBC and PMN%, in contrast with each test alone.

Author (Publication Year)	Synovial WBC (spec, sens)	Synovial PMN% (spec, sens)	Type I Boolean (spec, sens)	Type II Boolean (spec, sens)
Ghanem (2008)[37] knees	(0.881, 0.907) > 1100 WBC/μL YI = 0.788 PPV = 0.872 NPV = 0.915	(0.947, 0.950) > 64% YI = 0. 897 PPV = 0.916 NPV = 0.969	(0.992, 0.850) ↑↑ , ↓↓ YI = 0.842↑↓ PPV = 0.986↑↑ NPV = 0.916↑↓	(0.833, 0.975) ↓↓ , ↑↑ YI = 0.808↑↓ PPV = 0.780↓↓ NPV = 0.982↑↑
Chalmers (2014)[25] hips	(0.45, 0.98) > 745 WBC/μL YI = 0.43 PPV = 0.87 NPV = 0.86	(0.76, 0.90) > 73.5% YI = 0.66 PPV = 0.94 NPV = 0.67	(0.81, 0.90) ↑↑ , ↓→ YI = 0.71↑↑ PPV = 0.55↓↓ NPV = 0.97↑↑	(0.37, 0.98) ↓↓ , →↑ YI = 0.35↓↓ PPV = 0.29↓↓ NPV = 0.99↑↑
Chalmers (2014)[25] hips	(0.72, 0.92) > 1700 WBC/μL YI = 0.64 PPV = 0.93 NPV = 0.71	(0.35, 0.90) > 65% YI = 0.25 PPV = 0.91 NPV = 0.64	(0.82, 0.88) ↑↑ , ↓↓ YI = 0.70↑↑ PPV = 0.56↓↓ NPV = 0.97↑↑	(0.47*, 0.96) ↓↑ , ↑↑ YI = 0.43↓↑ PPV = 0.32↓↓ NPV = 0.98↑↑
Sousa (2017)[23] mixed hips and knees	(0.719, 1.000) > 1463 WBC/μL YI = 0.719 PPV = 0.719 NPV = 1.000	(0.750, 0.783) > 81% YI = 0.533 PPV = 0.692 NPV = 0.828	(0.750, 0.783) ↑→ , ↓→ YI = 0.533↓→ PPV = 0.692↓→ NPV = 0.828↓→	-
Pohlig (2017)[22] hips	Not reported Unknown cutoff	Not reported Unknown cutoff	-	(0.60, 0.80) YI = 0.40 PPV = 0.667 NPV = 0.75

*: Specificity of at least one test positive (serum WBC > 1700/μL, PMN% > 65%) in Chalmers 2014 violated inequality 2b for unknown reasons.

The arrows indicate the direction of sensitivity, specificity, YI, PPV, and NPV of a combination test in contrast with the first and second component tests (increased or decreased). YI: Youden's index = sensitivity + specificity - 1.

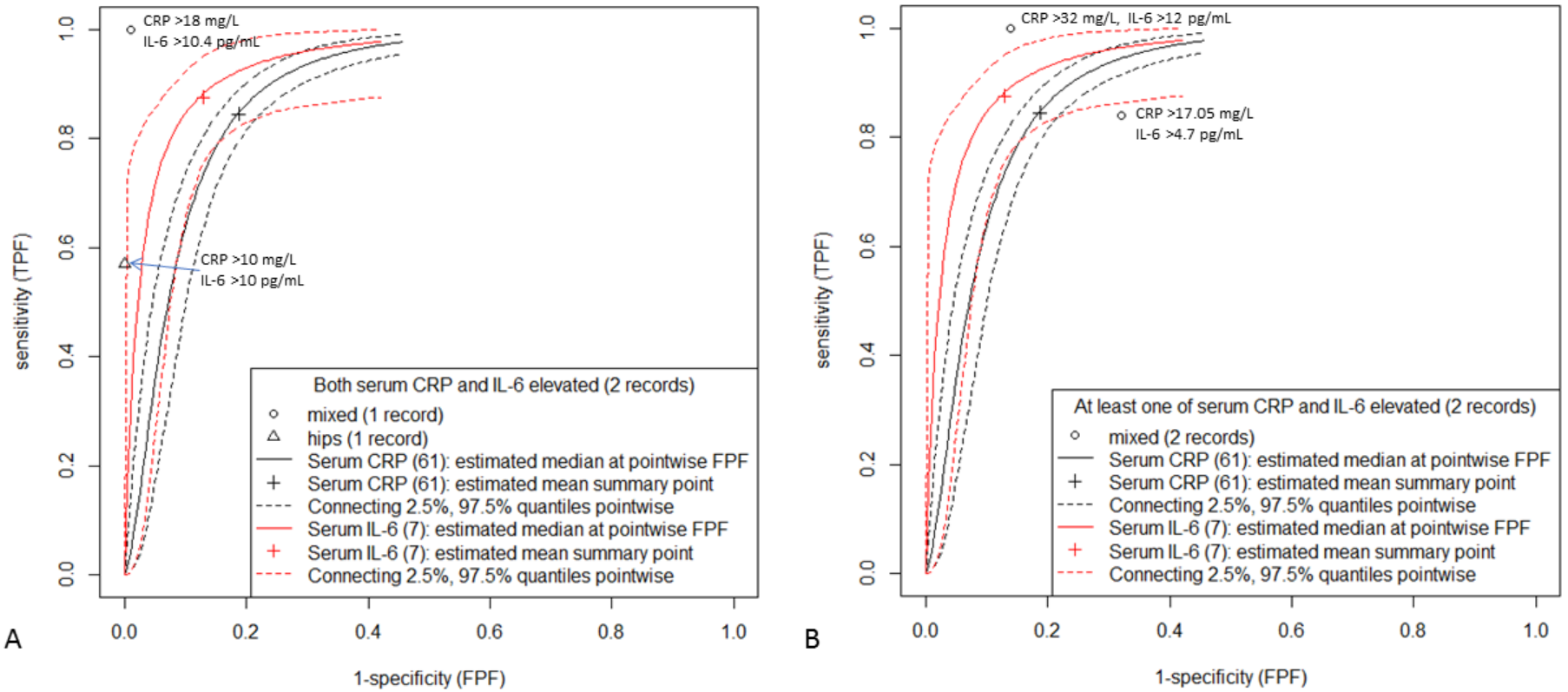
Type I Boolean combination: sensitivity = P(both tests positive | disease positive), and the corresponding specificity = P(at least one test negative | disease negative), while PPV = P(disease positive | both test positive) and NPV = P(disease negative | at least one test negative).

Type II Boolean combination: sensitivity = P(at least one test positive | disease positive), and the corresponding specificity = P(both tests negative | disease negative), while PPV = P(disease positive | at least one test positive) and NPV = P(disease negative | both tests negative).

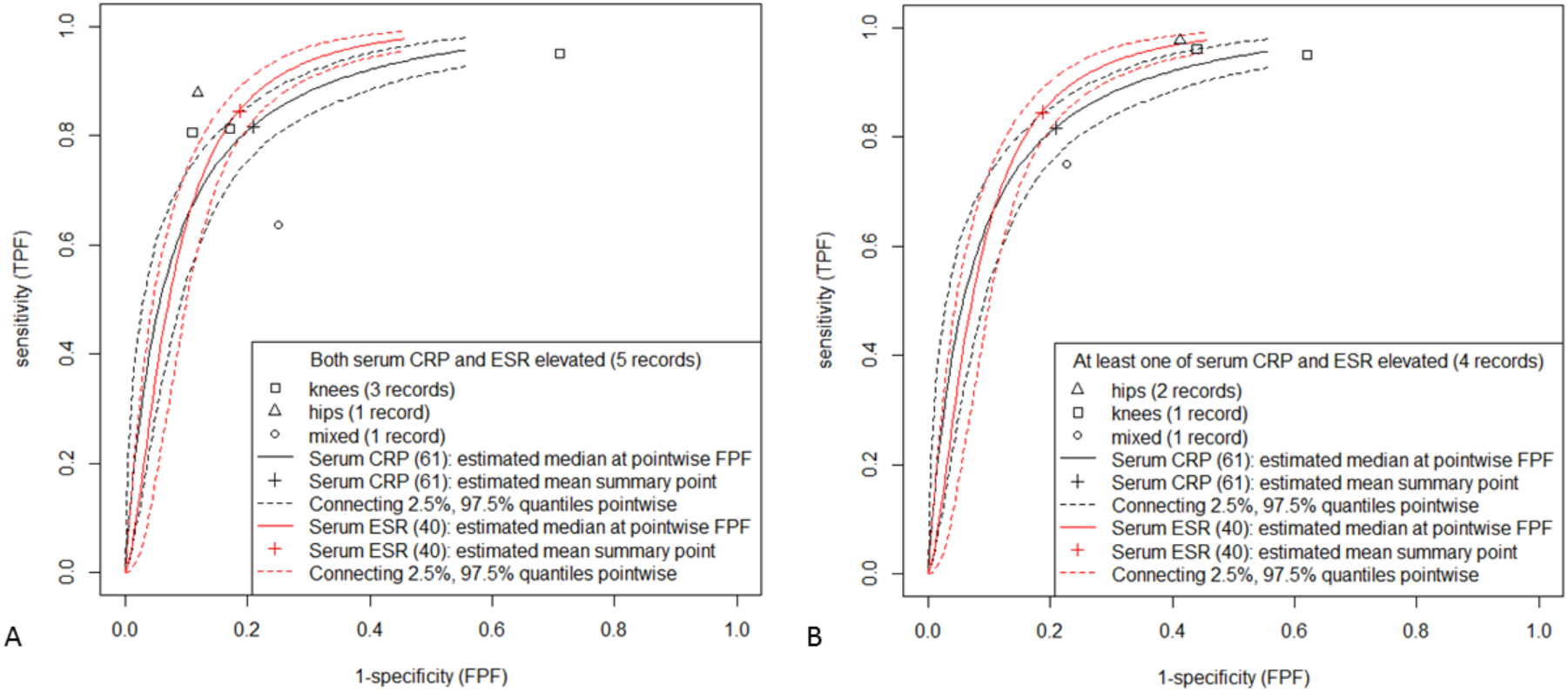
Additional Figures (eFigures 1-5)

The scatterplot for the accuracy of each of the eight combination tests (not meta-analyzed) were displayed together with the summary point and summary ROC curve of each test alone (from previous meta-analyses[4], and only serve an auxiliary purpose) in eFigures 1-5. We consider Tables 1-4 and Table A3 more valuable, because the accuracy of each test alone came from the same population of the combination test within each study.

eFigure 1: Scatterplots for the accuracy of (A) type I and (B) type II Boolean combinations of serum CRP and IL-6, displayed together with the summary point and the summary ROC curve of each test alone (from previous meta-analyses[4]). The number inside each parenthesis is the number of records.

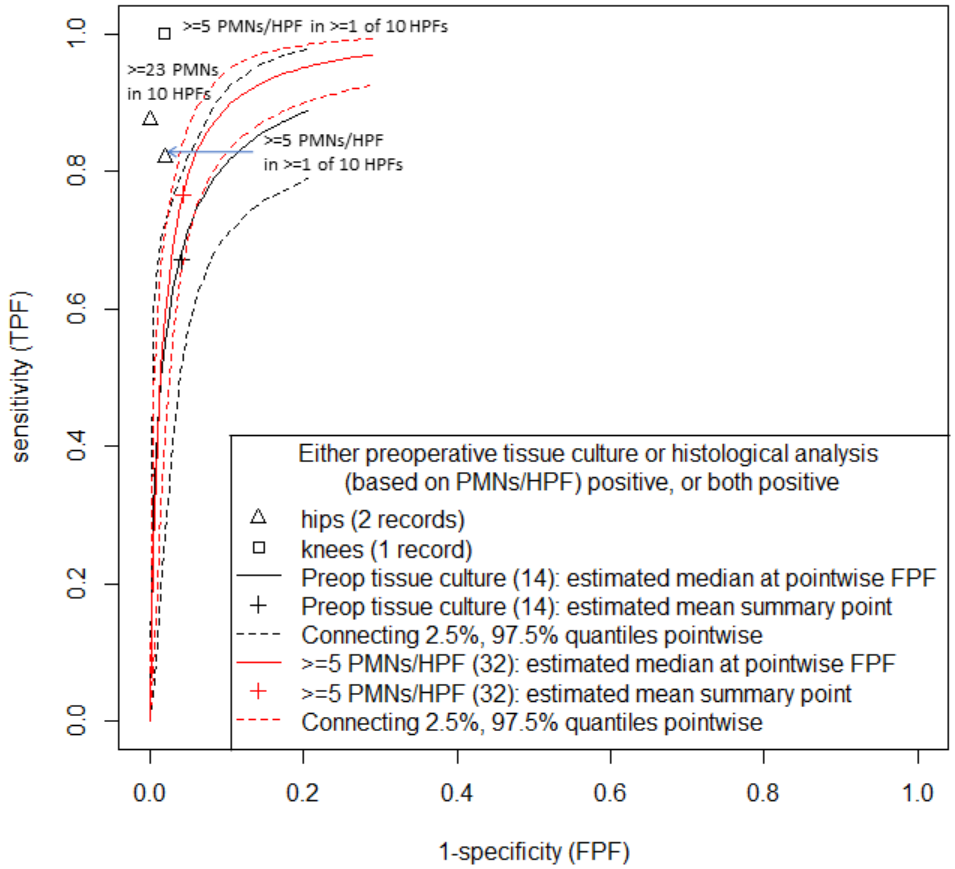


eFigure 2: Scatterplots for the accuracy of (A) type I and (B) type II Boolean combinations of serum CRP and ESR, displayed together with the HSROC curve and summary point of single test alone (from previous meta-analyses[4]). The number inside each parenthesis is the number of records.



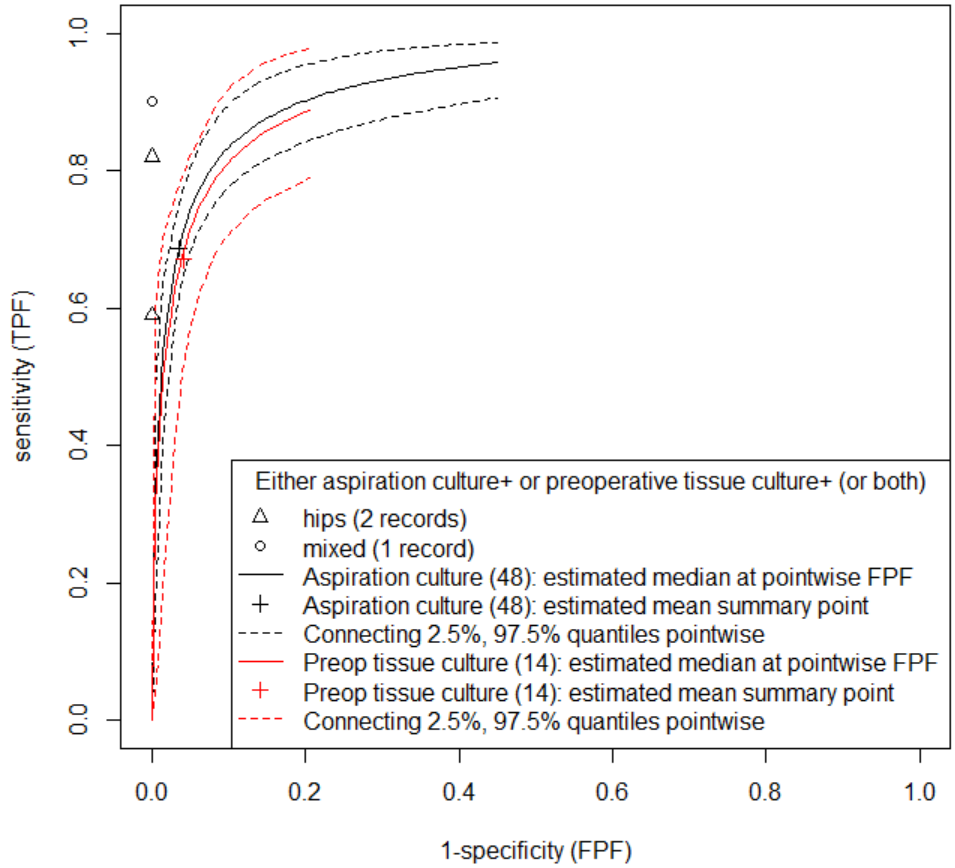
http://dx.doi.org/10.2106/JBJS.20.00097

eFigure 3: Scatterplot for the accuracy of either preoperative tissue culture or histological analysis based on PMNs positive (or both), displayed together with the summary point and the summary ROC curve of each test alone (from previous meta-analyses[4]). The number inside each parenthesis is the number of records. Tissue culture was regarded as positive if same organism was identified in >=2 samples.



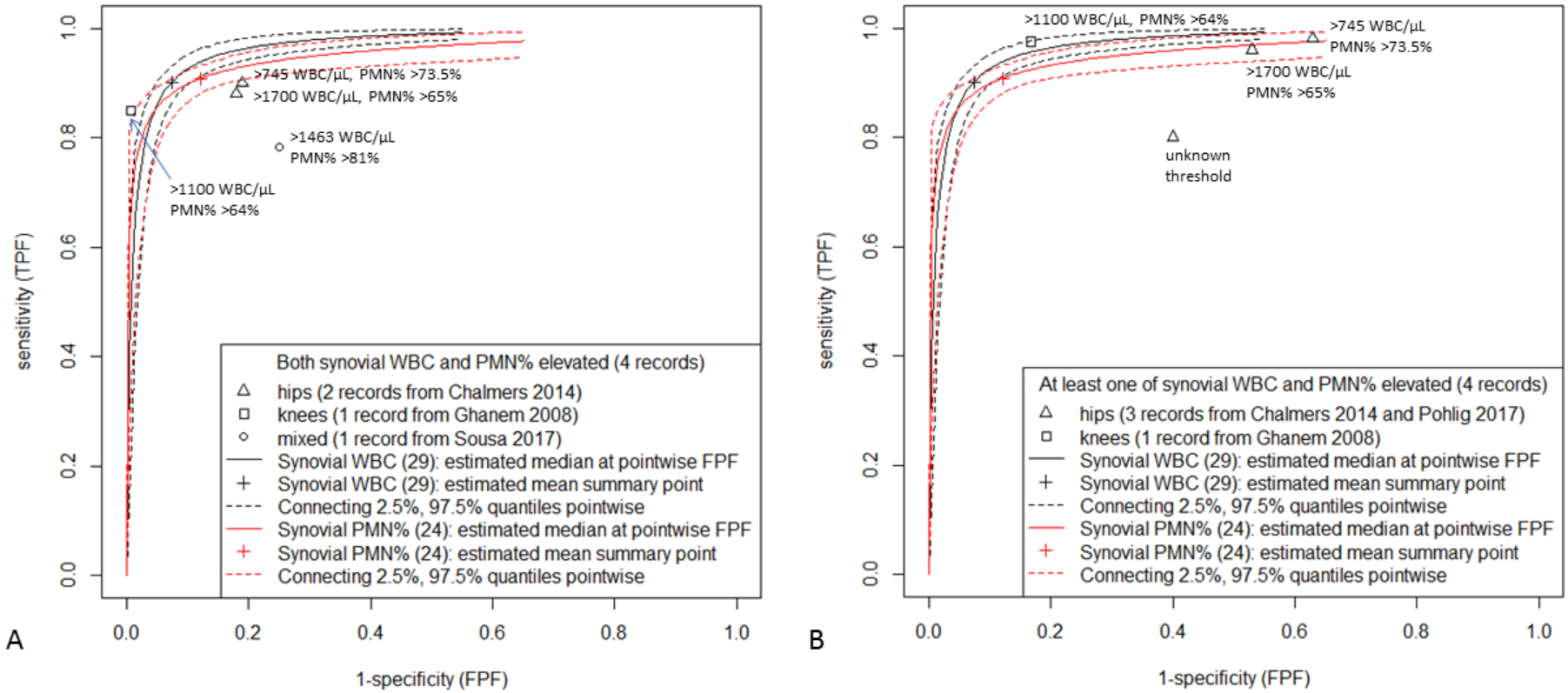
http://dx.doi.org/10.2106/JBJS.20.00097

eFigure 4: Scatterplot for the accuracy of either aspiration culture or preoperative tissue culture positive (or both), displayed together with the summary point and the summary ROC curve of each test alone (from previous meta-analyses[4]). The number inside each parenthesis is the number of records.



http://dx.doi.org/10.2106/JBJS.20.00097

eFigure 5: Scatterplots for the accuracy of (A) type I and (B) type II Boolean combinations of synovial WBC and PMN%, displayed together with the summary point and the summary ROC curve of each test alone (from previous meta-analyses[4]). The number inside each parenthesis is the number of records unless noted otherwise.



Appendix D: Stepwise clinical decision-making process for chronic PJI diagnosis, and detailed explanations

To initiate the process of a stepwise clinical decision-making for diagnosis, high sensitivity is required to minimize false negative (FN) findings. Based on the properties of combination tests, our proposed stepwise diagnosis starts with type II Boolean combination of serum CRP and IL-6 to reach higher sensitivity, and FN can be minimized especially when the thresholds were chosen such that each test reaches 90-95% sensitivity. Joint aspiration is next, if at least one of serum CRP and IL-6 is positive. If both serum tests are negative, other causes of joint pain such as metallosis, fracture, and soft tissue inflammation, etc., should be looked for. If joint aspiration is a wet tap, LER as a point-of-care synovial test should be used in priority, and if the reading is ++ or above, PJI has been confirmed; LER below ++ should be followed by one of the lab-based synovial tests, e.g., CRP, α-defensin, WBC, PMN%, and IL-6 (among them, synovial WBC and PMN% require more volume of synovial fluid compared to other synovial tests; in addition, WBC / PMN% might be uninterpretable due to bloody samples). If a lab-based synovial test is positive, PJI has been confirmed; if the lab-based synovial test is again negative, consider aseptic loosening or other causes of joint pain. If joint aspiration is a dry tap, a synovial biopsy is the next step with at least one of preoperative tissue culture and histological analysis (based on PMNs) confirms PJI. If preoperative tissue culture alone and histological analysis alone already have near-perfect specificity, use of type II combination may result in improved sensitivity while maintain the high specificity.

Detailed explanations of the stepwise clinical decision-making process

Not all component tests in the MSIS guideline are acquired at the same time. Although an aggregate score of the component tests in the 2018 definition of the MSIS guideline improved its strength to be used as the reference standard compared with previous versions, it does not outline how the proposed tests can be applied in stepwise clinical decision-making. As such, we would like to propose a stepwise clinical decision-making strategy for the diagnosis of chronic PJI. This appendix provides detailed explanations of the flow chart (Figure 2), organized in the three steps of diagnosis (serum, synovial, and tissue-based testing):

1. Beginning the screening process with type II Boolean combination of serum CRP and IL-6 will take at least the higher sensitivity of the two component tests, at the cost of taking the lower specificity of the two tests or below (Table 1).

   To tap the properties of type II Boolean combination, clinicians can calibrate the thresholds of serum CRP, IL-6 such that each of them reaches 90-95% sensitivity. Their type II Boolean combination will take the higher sensitivity of the two or above and thus minimize FN. The resulting lower specificity and possibly increased false positive (FP) findings can be contained in the synovial stage of stepwise diagnosis. The study by Bottner *et al.*[11] is a good example of this optimization strategy for deep infection; however, we think its thresholds of CRP >35 mg/L and IL-6 >12 pg/mL should be further verified in future studies.

   Alternatively, clinicians can make use of type I Boolean combination by choosing the thresholds of serum CRP, IL-6 such that each of them reaches almost 100% sensitivity. Their type I Boolean combination will bring about higher specificity without much loss of sensitivity as seen in the example of Elgeidi *et al.*[10] (however, its thresholds of CRP >18 mg/L and IL-6 >10.4 pg/mL did not always maintain both high sensitivity and specificity when applied to other studies in our published review of each test, and the optimal thresholds should be explored in more future studies).

   Joint aspiration is next if at least one of serum CRP and IL-6 is positive. If both serum tests are negative, other causes of joint pain such as metallosis, fracture, and soft tissue inflammation, etc., should be looked for. Trying to rule out these alternative causes one by one may take months, and if the joint is still painful, clinicians should send the patient for joint aspiration.

   Notes: 1). The usage of elevated CRP and ESR (CRP > 10 mg/L; ESR > 30 mm/hour) as one of the minor criteria in the 2013 MSIS guideline, if considered as type I Boolean combination in our definition, will lead to decreased sensitivity and more patients mistakenly judged as PJI negative than serum CRP alone (Table 1). Their type II Boolean combination could take the higher sensitivity of the two component tests or above at the cost of lower specificity.

   2). "Any of serum CRP, ESR, and D-Dimer positive" proposed by Shohat *et al.*[48] is not the only way to initiate the stepwise diagnosis. The sensitivity and specificity of serum IL-6 is as good as serum CRP[4] and better than other serum tests, and IL-6 has the response and normalization time to treatment for serum IL-6 is much quicker than ESR[46]. Therefore, we propose to use the type II combination of serum CRP and IL-6 instead.

   3). Triage-conditional combination provides an alternative approach (especially if cost of IL-6 test is a concern). We think ordering serum IL-6 only for patients with serum CRP ≤ 10 mg/L, as a triage-conditional rule, can also contain FN at the step of serum testing compared with CRP alone. The

threshold and the marginal benefit of adding serum IL-6 when serum CRP ≤ 10 mg/L should be quantified by future research based on individual level data.

2. Synovial aspiration: If joint aspiration is a wet tap, LER as a point-of-care synovial test should be used in priority, and if the reading is ++ or above, PJI has been confirmed; LER below ++ should be followed by one of the lab-based synovial tests, e.g., CRP, α-defensin, WBC, PMN%, and IL-6 (among them, synovial WBC and PMN% require more volume of synovial fluid compared to other synovial tests; in addition, WBC / PMN% might be uninterpretable due to bloody samples). If a lab-based synovial test is positive, PJI has been confirmed; if the lab-based synovial test is again negative, consider aseptic loosening or other causes of joint pain.

   Notes: 1). See Table 3 for studies reporting the use of "either aspiration culture or preoperative tissue culture positive". Given the low sensitivity of culture-based tests, it would be better to rely on the synovial tests which have good performance[4].

   2). See eTable A3 (Appendix C) for studies reporting Boolean combinations of synovial WBC and PMN%. It is not necessary to use type I or II Boolean combinations of synovial WBC and PMN% given the good performance of each test and the properties of Boolean combinations.

3. If joint aspiration is a dry tap, a synovial biopsy is the next step with at least one of preoperative tissue culture and histological analysis (based on PMNs) confirms PJI. Synovial biopsy could be taken at the same time of joint aspiration, but tissue culture is more time consuming than the synovial tests. If preoperative tissue culture alone and histological analysis alone already have near-perfect specificity, use of type II combination may result in improved sensitivity while maintain the high specificity (see Table 4). Identification of the microorganism from tissue culture helps to guide antibiotics therapy.

   If both preoperative tissue culture and histological analysis based on PMNs turn out to be negative, clinicians could find out the possibility that joint pain is triggered by aseptic loosening or other causes (such as metallosis, fracture, and soft tissue inflammation, etc).

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Appendix E: The checklist for stepwise diagnosis of chronic PJI

1. Did the patient arrive with a chronically painful primary THA / TKA?

For Yes:
- ☐ Primary total hip arthroplasty
- ☐ Primary total knee arthroplasty

For No:
- ☐ Not a primary joint arthroplasty
- ☐ Early postoperative (< 6 weeks)
- ☐ Other joint, please specify:

- ☐ Yes
- ☐ No

2. Please order both serum IL-6 and CRP for the patient. Were the values of both serum tests available for the patient?

Please record the values of
- ☐ Serum IL-6 level: pg/mL
- ☐ Serum CRP level: mg/L

Please choose the thresholds of serum IL-6 and CRP such that each of them reaches 90-95% sensitivity among the patients in your scenario:
- ☐ Threshold of serum IL-6: pg/mL
- ☐ Threshold of serum CRP: mg/L

- ☐ Yes, both were available
- ☐ Only serum IL-6
- ☐ Only serum CRP

3. Was at least one of serum IL-6 and CRP elevated according to the thresholds above?

Was serum IL-6 elevated?
- ☐ Yes
- ☐ No

Was serum CRP elevated?
- ☐ Yes
- ☐ No

- ☐ Yes → Question 4
- ☐ No, both tests negative → Question 10 (rule out other causes of joint pain)

4. Please perform synovial aspiration for the patient. Was it a wet tap?

- ☐ Wet tap → Question 5
- ☐ Dry tap → Question 7

5. If synovial aspiration was a wet tap, please use a point-of-care synovial test, LER strip.

LER is a point-of-care test and can give instant results. It turns out to be
- ☐ positive as defined by 2+ (++ or above, equivalent to ≥ 125 LE reading)
- ☐ negative (+ or below)

Alternatively, if point-of-care testing (e.g., LER strip, IL-6 or α-defensin lateral flow test) was not applied, please specify the reason:
- ☐ Point-of-care testing is available but skipped
- ☐ Point-of-care testing is not available

- ☐ Positive → **Revision of choice** + tissue culture to guide antibiotic treatment
- ☐ Negative → Question 6
- ☐ Not applied → Question 6

6. If a point-of-care test gave negative result or is not applied, please use a lab-based synovial test among CRP / IL-6 / WBC / PMN% / α-defensin. What was the finding?

Please select lab-based synovial test(s) which had been performed.
- ☐ CRP: threshold 6.9 mg/L ǂ
- ☐ α-defensin (ELISA): signal-to-cutoff ratio 1.0 ǂ
- ☐ WBC (if interpretable): threshold 3000 cells/μL for chronic PJI ǂ
- ☐ PMN% (if interpretable): threshold 80% for chronic PJI ǂ

- ☐ Positive → **Revision of choice** + tissue culture to guide antibiotic treatment
- ☐ Negative → Question 8

□ IL-6: no consensus regarding optimal threshold ǂ: According to 2018 definition of MSIS guideline
7. If synovial aspiration was a dry tap, please rely on synovial biopsy. (Otherwise, if revision of choice has been decided based on at least one of serum IL-6 and CRP positive followed by and a positive synovial test, tissue culture could be performed to guide antibiotic treatment.) **Were findings from both tissue culture and histological analysis available?**
Please make a record of the details: Tissue culture findings □ Available □ Not available Was tissue culture based on same pathogen isolated from >=2 separate tissue samples? □ Yes □ No (please specify): Histological analysis findings □ Available □ Not available Was histological analysis based on >=5 PMNs/HPF in at least 1 out of 5 high power fields? □ Yes □ No (please specify): □ Yes, both were available □ Only tissue culture □ Only histological analysis
8. Was at least one of tissue culture and histological analysis showing positive findings?
Was tissue culture positive? □ Yes □ No Was histological analysis positive? □ Yes □ No □ Yes, one or both tests were positive → **Revision of choice; use tissue culture to guide antibiotics treatment** □ No, both tests were negative → Question 8
9. If both tissue culture and histological analysis showed negative findings, it is up to the orthopaedic specialist to judge whether aseptic loosening was the causes of joint pain.
Was aseptic loosening the cause of joint pain? □ Yes → **No PJI** □ No → Question 9
10. Please rule out other causes of joint pain (may take ~ 2 months). Did you identify cause of joint pain other than PJI?
If the cause of joint pain other than PJI and aseptic loosening was identified, it was: □ Metallosis □ Fracture □ Soft tissue inflammation □ Other (please specify): □ Yes → **No PJI** □ No, causes other than PJI were not identified, but the joint is no longer painful → Tell the patient that neither PJI nor other causes were not identified □ No, the cause of joint pain was still unknown and the joint is still painful → Question 4: joint aspiration (with suspicion of progressive disease)