ONLINE SUPPLEMENT

Systematic review of diagnostic methods for Acute Respiratory Distress Syndrome

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On behalf of the DARTS consortium.

Content:

SUPPLEMENTAL METHODS

Search:

Exact search Medline:

(ARDS[title] OR "Acute respiratory distress syndrome"[title] OR ALI[title] OR "acute lung injury"[title]) AND (diagnosis OR diagnostic) AND (biomarker OR breath OR cytokine OR inflammation OR edema OR "lung water") AND (Humans[Mesh] AND adult[MeSH]) NOT review

Exact search Scopus:

(TITLE (ards) OR TITLE ("acute respiratory distress syndrome") OR TITLE (ali) OR TITLE ("acute lung injury") AND TITLE-ABS-KEY ((inflammation OR biomarker OR cytokine OR breath) OR (edema OR "lung water")) AND TITLE-ABS-KEY (diagnosis OR diagnostic)) AND (EXCLUDE (DOCTYPE , "re")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Humans") OR LIMIT-TO (EXACTKEYWORD , "Adult"))

CHECKLIST OF REPORTED ITEMS

Prisma checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
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.	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.	7
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.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S2
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).	7-9
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.	7-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-10

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.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
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.	8-9
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).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
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.	11
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.	12-15, S5-S11, S16-18
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).	16-22
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.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	S12-S15
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).	23-25
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).	25-26
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28
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.	28

N/A = not applicable.

ONLINE TABLES

Table S1:

Overview of all index tests.

Author	Test	Timing	Material	What is tested?	ROC	Sensitivity	Specificity	Cut-off	Unit	Bias
Abbas (1)	MBG/creatinine	Unclear.	Other	Pulmonary water	0.88	84	93	95	pg/mg	Intermediate
Aman (2)	Albumin	Within 12 hours after meeting sepsis criteria or 3 hours after major surgery.	Plasma	Permeability	0.8	79	64	17.05	g/L	Intermediate
	Transferrin				0.78	93	65	1.05	g/L	
Arif (3)	Transferrin	Within 72 hours after admission.	Plasma	Permeability	0.98	87	100	1.5	g/L	High
	Total protein			Permeability	0.9	81	87	56	g/L	
	Albumin			Permeability	0.77	44	100	24	g/L	
	PLI			Pulmonary water	0.98	87	100	16.3	$*10^{-3}$/min	
Bai (4)	Glutamate increase	At admission.	Plasma	Inflammation	0.79	N.D.	N.D.	99.89	µM	High
Bajwa (5)	sST2	Unclear.	Plasma	Inflammation	0.98	91	94	142	ng/mL	High
Bauer (6)	TNF-alfa	Within 24 hours after diagnosis.	Plasma	Inflammation	0.71	50	90	51.87	pg/mL	Low
	IL-1 beta				0.88	87	75	N.D.	N.D.	
	IL-6				0.61	96	35	14.81	pg/mL	
Bersten (7)	SP-A	Within 24 hours after inclusion.	Plasma	Permeability	0.61	N.D.	N.D.	N.D.	N.D.	Intermediate
	SP-B				0.77	85	78	4994	ng/mL	

Bos (8)	Three metabolites identified by GCMS	Unclear.	Breath	Oxidative stress	0.78	N.D.	N.D.	N/A	N/A	Low
Bos (9)	Pattern recognized by e-nose 1	Unclear.	Breath	Oxidative stress	0.71	N.D.	N.D.	N/A	N/A	Low
	Pattern recognized by e-nose 2				0.73	N.D.	N.D.	N/A	N/A	
Brett (10)	NO	After diagnosing ARDS. Or after intubation.	Breath	Inflammation	0.93	92	89	0.149	ppb	Intermediate
Bursten (11)	acyl ratio	Within 24 hours.	Plasma	Inflammation	N.D.	84	87	1.45	increase	Low
Copetti (12)	Alveolar interstitial syndrome	Unclear which time point used for test. Time points: at first day of admission and after diagnosis.	Other	Pulmonary water	N.D.	100	0	N/A	N/A	Intermediate
	Pleural line abnormalities				N.D.	100	45	N/A	N/A	
	Lung sliding				N.D.	100	100	N/A	N/A	
	Spared areas				N.D.	100	100	N/A	N/A	
	Consolidations				N.D.	83.3	100	N/A	N/A	
	Pleural effusion				N.D.	66.6	5	N/A	N/A	
	Lung pulse				N.D.	50	100	N/A	N/A	
Determann (13)	CC16	On day of diagnosis.	Plasma	Inflammation	0.91	80	92	18	ng/mL	High
	CC16 increase			Inflammation	N.D.	90	92	0.3	increase	

	KL-6			Inflammation	0.71	N.D.	N.D.	N.D.	N.D.	
	sRAGE			Inflammation	0.63	N.D.	N.D.	N.D.	N.D.	
	SP-D			Permeability	0.8	N.D.	N.D.	N.D.	N.D.	
El Solh (14)	PAI-1	Within 8 hours after intubation	Alveolar fluid	Coagulation	0.93	82.4	97.1	1518	ng/mL	Intermediate
	PAI-1		Plasma		0.65	N.D.	N.D.	N.D.	N.D.	
Fremont (15)	Model with 7 biomarkers (RAGE, PCPIII, BNP, ANG2, IL-10, TNF-alfa, IL-8)	Within 72 hours after admission.	Plasma	Inflammation	0.86	N.D.	N.D.	N/A	N/A	High
	Model with 3 biomarkers				0.83	N.D.	N.D.	N/A	N/A	
Grissom (16)	PAF-AH	Within 96 after diagnosis.	Alveolar fluid	Inflammation	0.83	63	100	37.87	mU/mL	High
Herrera (17)	PPK	Within 24 hours after diagnosis.	Plasma	Permeability	0.9	83	100	78.15	Ratio	Intermediate
Hoeboer (18)	Albumin	Within 24 hours after fever onset.	Plasma	Inflammation	0.62	71	58	20	g/L	Low
Howrylak (19)	Genetic model	Within 48 hours after admission.	Plasma	Inflammation	0.89	100	50	N/A	N/A	Intermediate
Huang (20)	IG percentage	At admission.	Plasma	Inflammation	0.821	N.D.	N.D.	N.D.	N.D.	Intermediate
Izquierdo-Garcia (21)	Metabolic biomarker panel	Within 24 hours after admission.	Plasma	Inflammation	N.D.	100	91	N/A	N/A	High
Jabaudon (22)	sRage0	At admission.	Plasma	Permeability	0.71	N.D.	N.D.	N.D.	N.D.	Low

	sRage1	24 hours after admission.			0.79	N.D.	N.D.	N.D.	N.D.	
	sRage1-0				0.63	N.D.	N.D.	N.D.	N.D.	
Jorens (23)	IL-8	Within 12 hours after diagnosis.	Alveolar fluid	Inflammation	0.63	0.73	0.67	299.3	pg/mL	Intermediate
Kietzmann (24)	maximum H2O2	Within the first 7 days.	Breath	Inflammation	0.7	0.71	0.84	468.6	nmol/L	High
Kushimoto (25)	PVPI	On day of enrollment, within 5 days after onset of acute respiratory failure.	Other	Permeability	0.886	N.D.	N.D.	N.D.	N.D.	Low
	ITBV			Pulmonary water	0.471	N.D.	N.D.	N.D.	N.D.	
LeTourneau (26)	EVLWi	Within 48 hours after meeting ARDS criteria.	Other	Pulmonary water	0.75	63	88	10	ml/kg PBW	Intermediate
	PaO2/FiO2				0.71	N.D.	N.D.	N.D.	N.D.	
	EDI				0.77	N.D.	N.D.	N.D.	N.D.	
Lin (27)	Copeptin	Within 12 hours after admission.	Plasma	Inflammation	0.823	60.9	88.2	40.11	pmol/L	Low
Lin (28)	HBP	After diagnosis.	Plasma	Permeability	0.815	75	78.2	11.55	ng/mL	Low
Lin (29)	CC16	Within 12 hours after admission.	Plasma	Inflammation	0.911	90.4	79.8	33.3	ng/mL	Low
	CRP				0.648	54.4	73.2	N.D.	N.D.	
Liu (30)	MDA	Two hours after graft reperfusion.	Breath	Oxidative stress	0.88	N.D.	N.D.	N.D.	N.D.	High
	NO			Oxidative stress	0.88	N.D.	N.D.	N.D.	N.D.	
	H2O2			Oxidative stress	0.78	N.D.	N.D.	N.D.	N.D.	

	8-isoprostaglandin F2 alfa			Oxidative stress	0.84	N.D.	N.D.	N.D.	N.D.	
	TNF-alfa			Inflammation	0.84	N.D.	N.D.	N.D.	N.D.	
	IL-8			Inflammation	0.94	N.D.	N.D.	N.D.	N.D.	
	SOD			Oxidative stress	0.81	N.D.	N.D.	N.D.	N.D.	
	IL-10			Inflammation	0.84	N.D.	N.D.	N.D.	N.D.	
Liu (31)	PARK7	At admission.	Plasma	Oxidative stress	0.73	78	70	200	ng/mL	Intermediate
Monnet (32)	PVPI	At diagnosis of oedema.	Other	Permeability	0.92	85	100	3	N/A	Intermediate
	EVLWi/GEDVi			Pulmonary water	0.92	85	100	$1.8*10^{-2}$	N/A	
Park (33)	SP-D	Within 72 hours after admission.	Plasma	Inflammation	0.71	74	63	12.7	ng/mL	High
Sato (34)	KL-6	Up to a week after diagnosis.	Plasma	Inflammation	0.9	75	100	393.75	U/mL	High
Sekiguchi (35)	CCUS prediction model	Within 4 hours after inclusion.	Other	Pulmonary water	0.79	N.D.	N.D.	≤3	N/A	Low
Shan (36)	suPAR	After diagnosis.	Plasma	Inflammation	0.63	N.D.	N.D.	N.D.	pg/mL	Intermediate
	hsCRP				0.65	N.D.	N.D.	N.D.	N.D.	
	PCT				0.72	N.D.	N.D.	N.D.	N.D.	
Sweeney (37)	Model with seven genes	Within 48 hours after diagnosis.	Plasma	Inflammation	0.74	63	74	N/A	N/A	High
Verheij (38)	PLI	Within 72 hours after admission.	Other	Permeability	0.94	N.D.	N.D.	N.D.	N.D.	High
	PTCER				0.96	N.D.	N.D.	N.D.	N.D.	

	Ga/Tc slope/intercept				0.89	N.D.	N.D.	N.D.	N.D.	
	Ga/Tc monoexponential TER				0.82	N.D.	N.D.	N.D.	N.D.	
Ware (39)	Model with 5 biomarkers (SP-D, RAGE, IL-8, CC16, IL-6)	On day 2.	Plasma	Inflammation	0.75	70	68	N/A	N/A	Low
Ware (40)	Model with 11 biomarkers	Within 72 hours after admission.	Plasma	Inflammation	0.78	N.D.	N.D.	N/A	N/A	Intermediate
	Model with 2 biomarkers (ang-2 and RaGE)				0.74	N.D.	N.D.	N/A	N/A	
Wu (41)	CC16	Within 24 hours.	Plasma	Inflammation	0.8	91	60	16.8	ng/mL	Intermediate
Xue (42)	Tissue factor	At inclusion.	Plasma	Permeability	0.75	61.7	80.8	1005.8	pg/mL	Intermediate
Yeh (43)	Gas6	Within 24 hours after admission.	Plasma	Inflammation	0.74	78	72	18	ng/mL	Low
Zhou (44)	Panel with 9 metabolites	Unclear.	Breath	Inflammation	0.82	N.D.	N.D.	N/A	N/A	Low

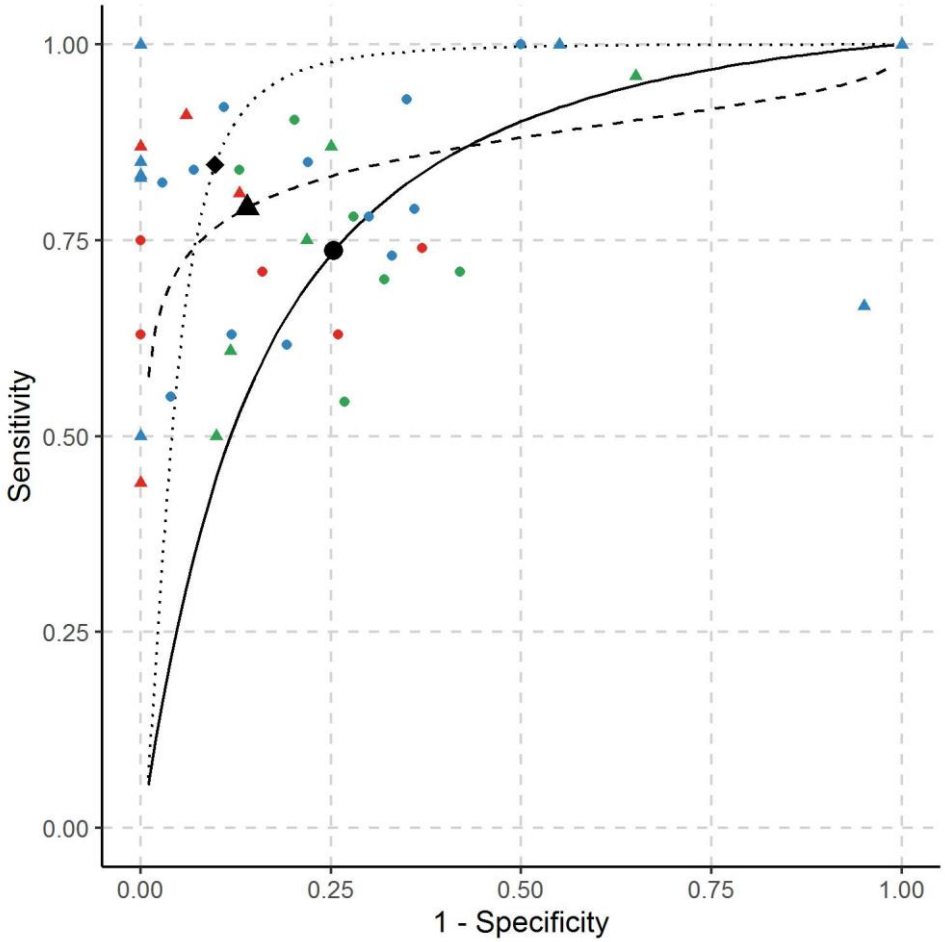
N/A= not applicable. N.D.= not described.

Abbreviations (in alphabetical order): AECC = American-European consensus criteria, ARDS = Acute Respiratory Distress Syndrome, CC16 = Club Cell protein 16, CCUS = critical care ultrasonography, CPE = cardiac pulmonary oedema, CRP = c-reactive protein, EDI = EVLW physiologic dead space index, EVLW = extra vascular lung water, Gas6 = growth arrest-specific gene 6 , Ga/Tc = gallium/technetium , GCMS=gas chromatography mass spectrometry, H2O2 = hydrogen peroxide, HBP =

heparin-binding protein, hsCRP = high sensitive c-reactive protein, ICU = intensive care unit, IG = immature granulocyte, IL = interleukin, ITBV = intrathoracic blood volume, KL = Krebs von den Lungen, MDA = malondialdehyde, NO = nitric oxide, PAF-AH = platelet-activating factor acetylhydrolase, PAI-1 = plasminogen activator inhibitor-1, PARK7 = Parkinson disease 7 , PCT = procalcitonin, PLI = pulmonary leak index, PPK = prekallikrein, PTCER = pulmonary transcapillary escape rate, PVPI = extravascular lung water/pulmonary blood volume, SOD = superoxide dismutase, SP = surfactant protein, sRAGE = soluble receptor for advanced glycation end-products, sST2 = soluble suppression of tumorigenicity-2, suPAR = soluble urokinase-type plasminogen activator receptor, TER = transcapillary escape rate, TNF = tumor necrosis factor.

ONLINE FIGURES

Figure S1: Sensitivity and specificity, stratified per control group



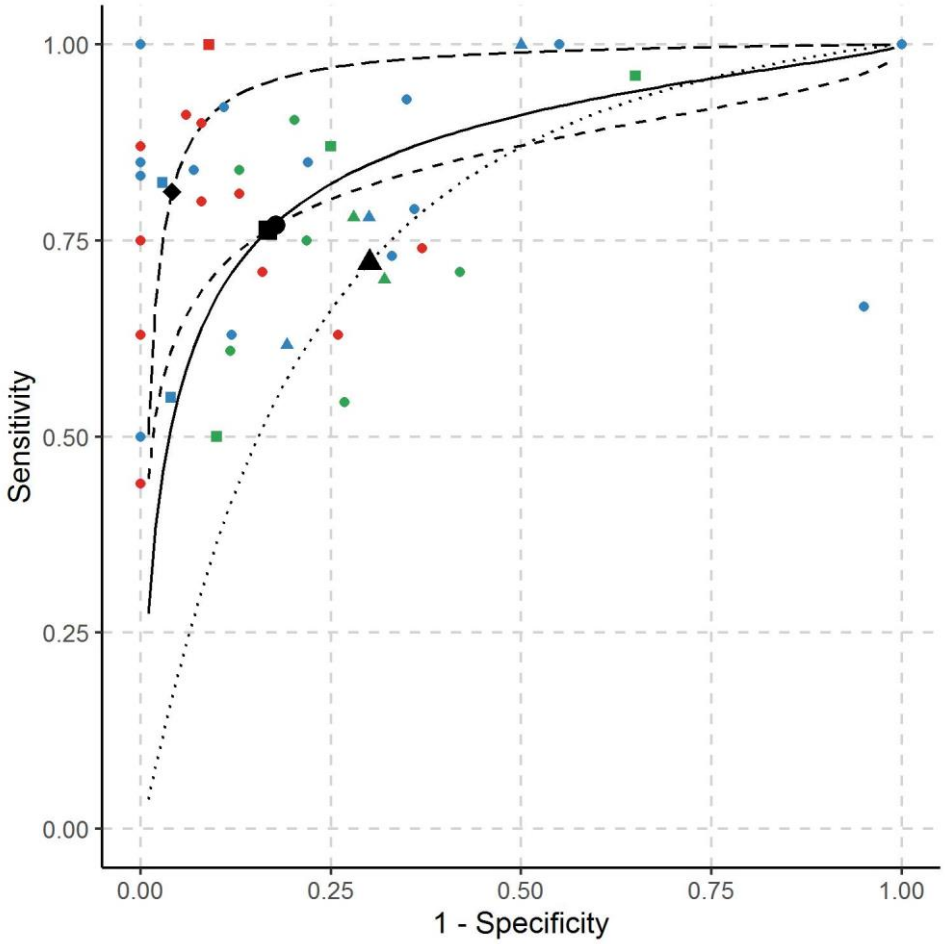
Triangle: CPE (n=20)

Circle: ICU all (n=24)

Diamond: Pneumonia (n=3)

Green: low bias. Blue: intermediate bias. Red: high bias.

Figure S2: Sensitivity and specificity, stratified per population



Triangle: Sepsis (n=6)

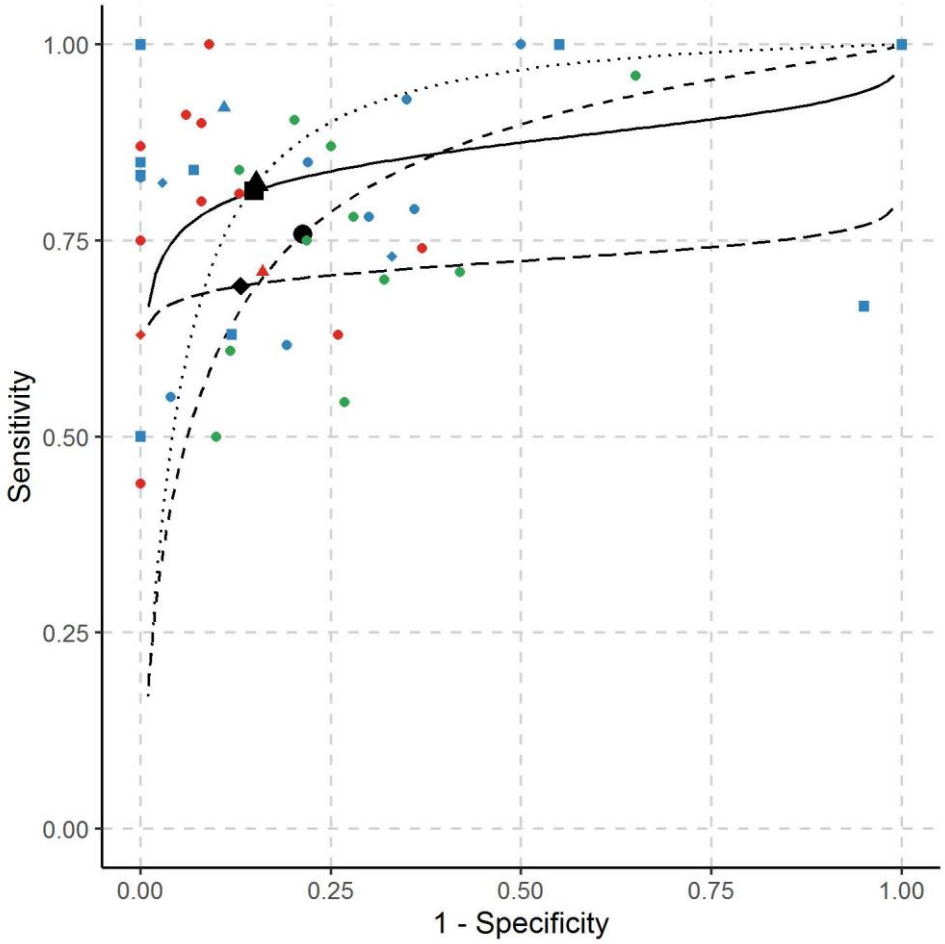
Circle: ICU general (n=34)

Square: Specific group (n=6)

Diamond: CCU (n=1)

Green: low bias. Blue: intermediate bias. Red: high bias.

Figure S3: Sensitivity and specificity, stratified per material



Triangle: Breath (n=2)

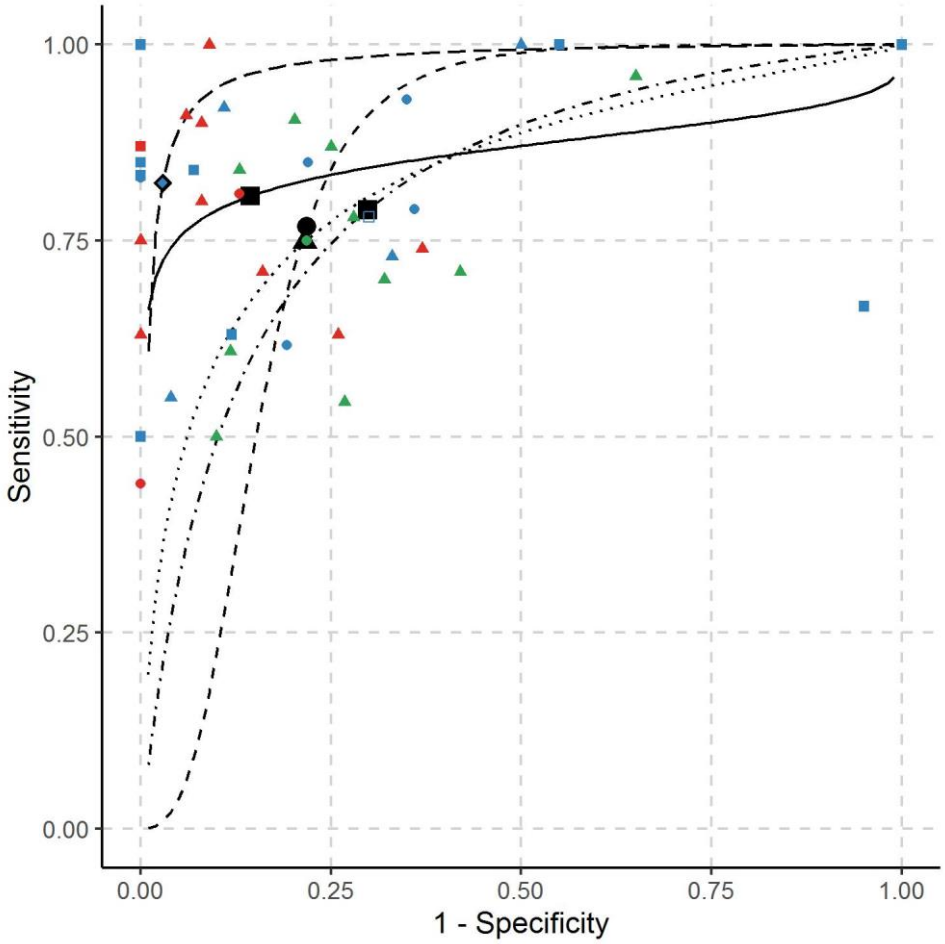
Circle: Plasma (n=31)

Square: Other (n=11)

Diamond: Alveolar fluid (n=3)

Green: low bias. Blue: intermediate bias. Red: high bias.

Figure S4: Sensitivity and specificity, stratified per mechanism



Triangle: Inflammation (n=23)

Circle: Permeability (n=10)

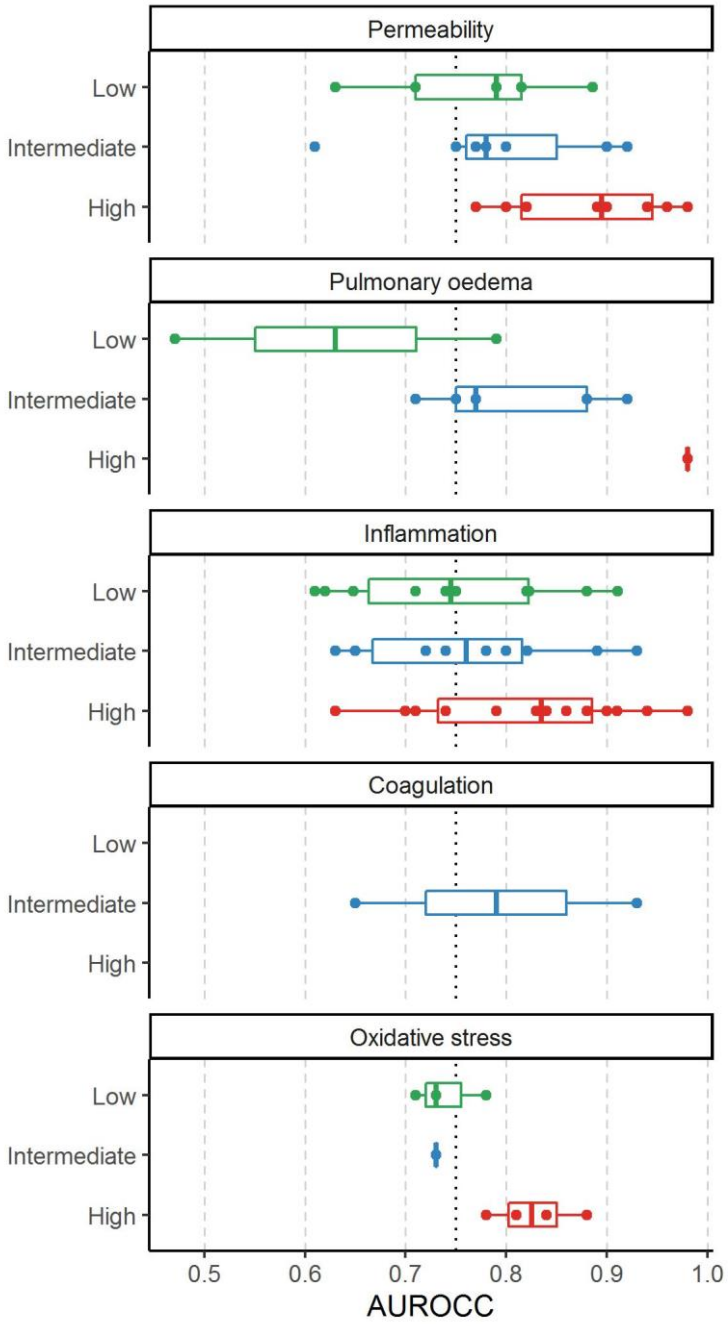
Filled square (solid line): Pulmonary oedema (n=11)

Diamond: Coagulation (n=1)

Open square (dot-dash line): Oxidative stress (n=1)

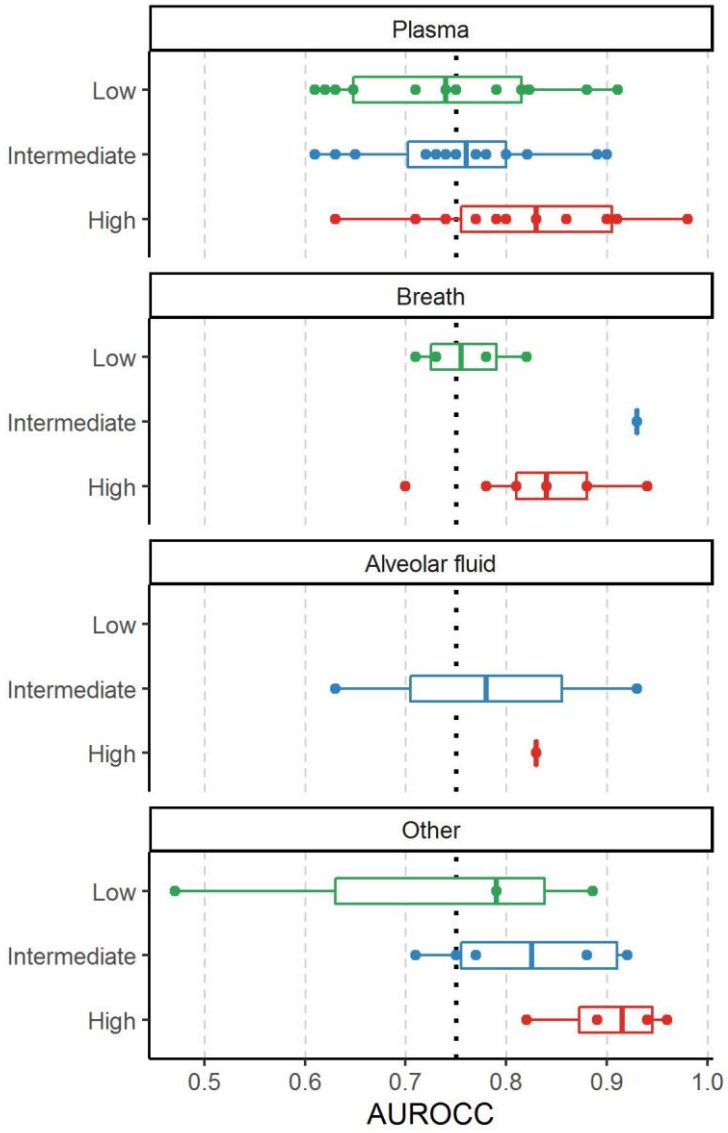
Green: low bias. Blue: intermediate bias. Red: high bias.

Figure S5: Association between risk of bias and diagnostic accuracy, stratified per type of process measured by the test.



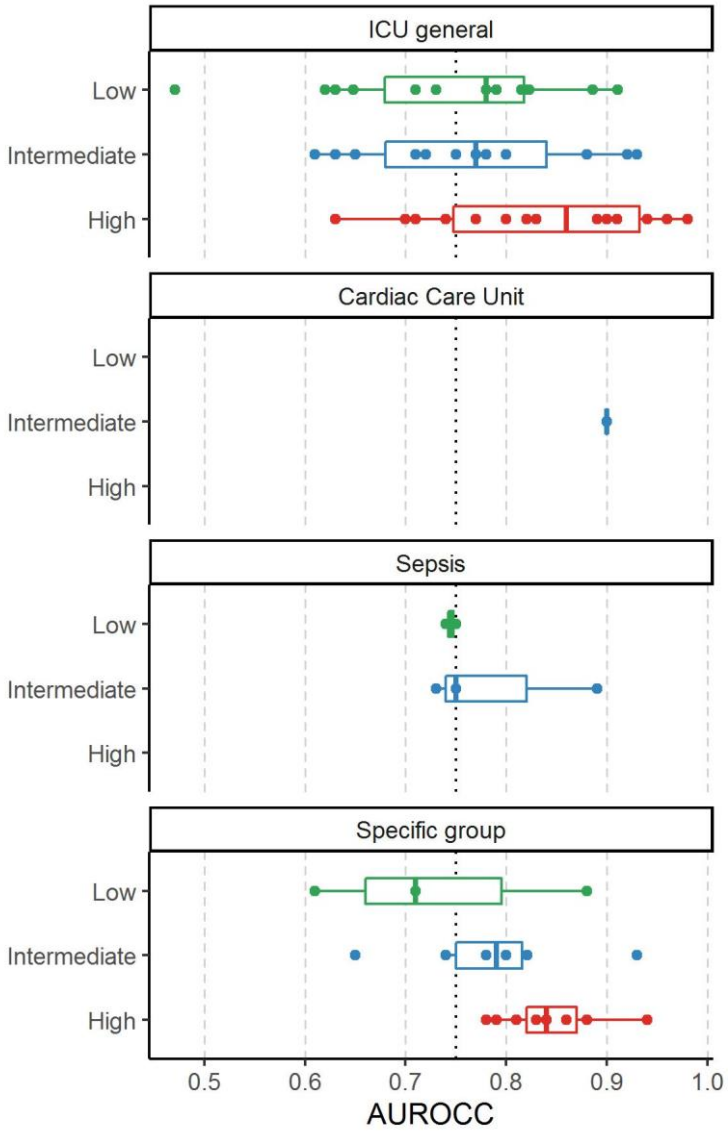
Caption: AUROCC = area under the receiver operating characteristics curve. No difference in AUROCC was found for the type of studied pathophysiological mechanism (p=0.76).

Figure S6: Association between risk of bias and diagnostic accuracy, stratified per tested biomaterial.



Caption: AUROCC = area under the receiver operating characteristics curve. No difference in AUROCC was found for the used material (p=0.51).

Figure S7: Association between risk of bias and diagnostic accuracy, stratified per included population.



Caption: AUROCC = area under the receiver operating characteristics curve. No difference in AUROCC was found for the different populations (p=0.60).

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