Appendix for:

Biomarkers for Prediction of Renal Replacement Therapy in Acute Kidney Injury: A Systematic Review and Meta-Analysis

1. Search Strategies

Embase

Embase search strategy:

- 1 biomarker (139901)
- 2 NGAL OR neutrophil gelatinase-associated lipocalin OR neutrophil gelatinase associated lipocalin (6910)
- 3 KIM-1 OR kidney injury molecule-1 (1462)
- 4 cystatin c OR cystatin-c (9633)
- 5 L-FABP OR fatty acid-binding protein 1 (1049)
- 6 IL-18 OR interleukin-18 or interleukin 18 (17305)
- 7 IGFBP7 OR IGF-binding protein-7 OR IGF binding protein 7 (433)
- 8 TIMP2 OR tissue inhibitor metalloproteinase-2 (1029)
- 9 calprotectin (3997)
- 10 CAF OR c-terminal agrin fragment OR c terminal agrin fragment (4427)
- 11 L1 OR L2 OR L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10
- 12 AKI OR acute kidney injury OR acute kidney failure OR acute renal failure (80015)
- 13 RRT or renal replacement therapy or ?dialysis OR CVVH? OR (hemofiltration OR haemofiltration) OR (CRRT OR continuous renal replacement therapy) (279067)
- 14 L11 AND L12 AND L13 (947)
- 15 L14 NOT MEDLINE/FS (913)
- 16 L14 NOT REVIEW/DT (752)

752 Search results Results obtained September 19, 2017

Pubmed

Pubmed/NIH search strategy:

(biomarker

OR (NGAL OR "Neutrophil gelatinase-associated lipocalin" OR "Neutrophil gelatinase associated lipocalin") OR (KIM-1 OR "Kidney Injury Molecule-1") OR ("Cystatin C" OR "Cystatin-C") OR (L-FABP OR "Fatty acid-binding protein 1") OR (IL-18 OR "Interleukin-18" OR "Interleukin 18") OR (IGFBP7 OR "IGF-Binding Protein-7" OR "IGF Binding Protein 7") OR (TIMP2 OR "Tissue Inhibitor Metalloproteinase-2") OR Calprotectin OR (CAF OR "c-terminal agrin fragment" OR "c terminal agrin fragment"))

AND (aki OR "acute kidney injury" OR "acute kidney failure" OR "acute renal failure") AND (rrt OR "renal replacement therapy" OR *dialysis OR CVVH* OR (hemofiltration OR haemofiltration) OR (CRRT OR "continous renal replacement therapy")) NOT Review[ptyp]

656 Search results Results obtained September 19, 2017

CENTRAL

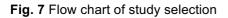
CENTRAL search strategy:

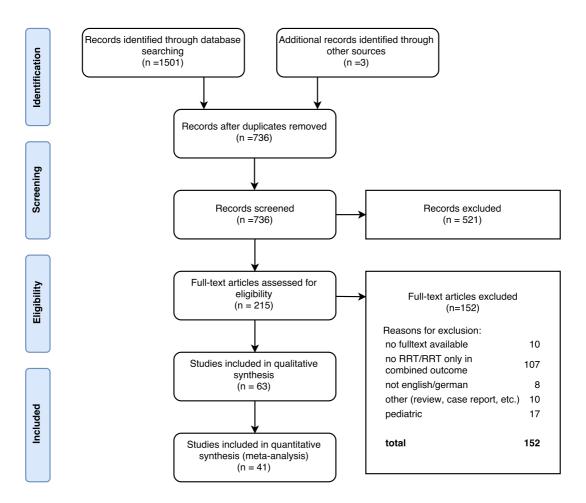
- ID Search Hits
- #1 biomarker 5980
- #2 (NGAL or "Neutrophil gelatinase-associated lipocalin" or "Neutrophil gelatinase associated lipocalin") 370
- #3 (KIM-1 or "Kidney Injury Molecule-1") 113
- #4 ("Cystatin C" or "Cystatin-C") 516
- #5 (L-FABP or "Fatty acid-binding protein 1") 54
- #6 (IL-18 or "Interleukin-18" or "Interleukin 18") 392
- #7 (IGFBP7 or "IGF-Binding Protein-7" or "IGF Binding Protein 7") 17
- #8 (TIMP2 or "Tissue Inhibitor Metalloproteinase-2" or TIMP-2) 70
- #9 Calprotectin 325
- #10 (CAF or "c-terminal agrin fragment" or "c terminal agrin fragment") 541
- #11 (aki or "acute kidney injury" or "acute kidney failure" or "acute renal failure") 3179
- #12 (rrt or "renal replacement therapy" or *dialysis or CVVH* or (hemofiltration or haemofiltration) or (CRRT or "continous renal replacement therapy"))
 15562
- #13 #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 2163
- #14 #1 or #13 7962
- #15 #14 and #11 and #12 115

115 Search results (93 Trials, 1 Econ. Eval., 21 Reviews excluded) Results obtained September 19, 2017

2. Supplemental figures and tables

2.1. Supplemental figures and tables for the study selection and QUADAS-2 risk of bias assessment





QUADAS-2 risk of bias assessment (Fig.8 and Tab.2)

QUADAS-2 risk of bias assessment is performed in four domains:

Risk of bias in the domain 'patient selection' evaluated the methods of patient selection (e.g. if a consecutive or random sample of patients was enrolled or if the study avoided inappropriate exclusions); the applicability judgment was based on whether there was concern that the included patients matched the review question or not.

Risk of bias in the domain 'index test' states, whether there was concern that the conduct and interpretation (e.g. if the laboratory personal was blinded to the patient's condition) of the index test lead to possible bias, while the applicability judgment was based on whether there was concern that the index test, its conduct or the interpretation differed from the review question or not.

The domain 'RRT initiation' states whether there was a possible risk of bias regarding the initiation of RRT (eg. what criteria were used to classify the need for RRT initiation and if the decision to initiate RRT was made without knowledge of the biomarker results). The applicability judgment in this domain was based on whether there was concern that the initiation of RRT matched the review question.

In the domain 'flow and timing' judgment for risk of bias was based on whether there was concern if e.g. some patients were excluded from the analysis or if there was an appropriate interval between critical illness and RRT.

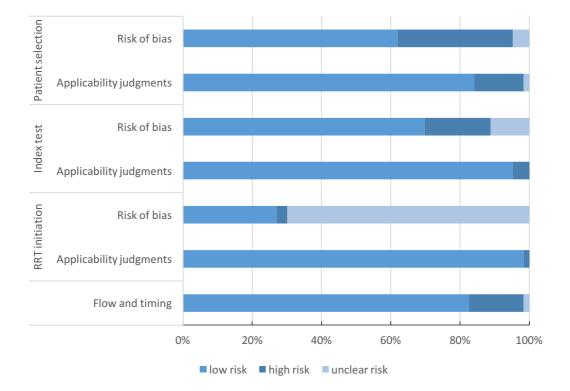


Fig. 8 Results of the QUADAS-2 risk of bias assessment.

Tab. 2 Results of the	QUADAS-2 risk of bias assessment
-----------------------	----------------------------------

	-	Patient selection Index Test						
Author/Maar	Risk of	Applicability	Risk of	Applicability	Risk of	Applicability	Flow	
Author/Year	bias	judgements	bias	judgements	bias	judgements	Timin	
Albeladi et al. 2017 [28]	low	low	low	low	low	low	Low	
Alge et al. 2013 [59]	low	low	high	high	high	low	Low	
Bagshaw et al. 2010 [29]	low	low	high	low	high	low	low	
Cemil et al. 2014 [19]	high	low	high	low	low	low	high	
Chun et al. 2017 [80]	low	low	unclear	low	unclear	low	low	
Constantin et al. 2010 [30]	low	low	low	low	unclear	low	low	
Cruz et al. 2009 [31]	low	low	low	low	unclear	low	low	
de Geus et al. 2011 [32]	low	low	low	low	unclear	low	low	
Dihazi et al. 2016 [33]	low	low	low	low	low	low	low	
Drey et al. 2015 [75]	low	low	high	low	unclear	low	low	
Du et al. 2013 [60]	high	low	high	low	unclear	low	low	
Dusse et al. 2016 [64]	low	low	low	low	unclear	low	low	
Endre et al. 2010 [35]	low	low	low	high	unclear	low	low	
Endre et al. 2011 [34]	low	low	low	high	unclear	low	low	
Gaipov et al. 2015 [67] Garcia-Alvarez et al. 2015	low	low	high	low	unclear	low	low	
61]	low	low	high	low	unclear	low	high	
Glassford et al. 2013 [36]	low	low	low	low	unclear	low	low	
Gocze et al. 2015 [68]	low	low	low	low	unclear	low	low	
laase-Fielitz et al. 2009 [65]	high	low	low	low	low	low	high	
laase-Fielitz et al. 2011 [62]	high	low	low	low	low	low	low	
Haines et al. 2017 [37]	low	low	low	low	unclear	low	low	
lanson et al. 2011 [77]	high	high	high	low	low	low	low	
lerget-Rosenthal et al. 2004	-	-	-					
38] Ierget-Rosenthal et al. 2004	low	low	low	low	unclear	low	low	
20]	low	low	low	low	low	low	low	
ljortrup et al. 2015 [74]	high	unclear	low	low	unclear	low	low	
lo et al. 2017 [21]	low	low	unclear	low	unclear	low	low	
lu et al. 2017 [70]	low	low	low	low	unclear	low	low	
enov et al. 2016 [39]	high	low	low	low	unclear	low	low	
alkanen et al. 2013[40]	low	low	high	low	unclear	low	low	
Kiessling et al. 2014[58]	high	high	low	low	low	low	low	
(im et al. 2017 [76]	low	low	low	low	unclear	low	low	
Koyner et al. 2015 [41]	high	low	low	low	unclear	low	low	
Koziolek et al. 2012 [42]	low	low	high	low	low	low	low	
inko et al. 2013 [43]	high	high	low	low	unclear	low	high	
ukasz et al. 2014 [79]	low	high	low	low	unclear	low	low	
/lahdavi-Mazdeh et al. 2012 73]	hiah	high	low	low	low	high	low	
	high	high	low	low	low	high	low	
/aisel et al. 2016 [22]	low	low	low	low	unclear	low	low	
lårtensson et al. 2017 [44]	low	low	low	low	unclear	low	low	
Acliroy et al. 2015 [66]	high	low	low	low	unclear	low	low	
Vejat et al. 2010 [45]	high	high	low	low	unclear	low	high	
lisula et al. 2014 [46]	low	low	low	low	unclear	low	low	
lisula et al. 2015 [47]	low	low	low	low	unclear	low	low	
D'Sullivan et al. 2017 [48]	high	low	low	low	unclear	low	low	
Park et al. 2013 [23]	low	low	low	low	low	low	low	
Pianta et al. 2015 [72]	high	high	unclear	low	low	low	low	
Pickering et al. 2012 [50]	low	low	low	low	unclear	low	uncle	
Pickering et al. 2013 [49]	high	low	low	low	unclear	low	high	
Pipili et al. 2014 [51]	high	low	unclear	low	low	low	low	
Plewes et al. 2017 [78]	low	high	low	low	low	low	low	
alib et al. 2012 [52]	low	low	low	low	unclear	low	high	
Renhua et al. 2014 [24]	high	low	low	low	unclear	low	low	
Rewa et al. 2015 [25]	low	low	high	low	unclear	low	high	
Royakkers et al. 2011 [54]	high	low	low	low	unclear	low	low	
Royakkers et al. 2012 [53]	high	low	low	low	low	low	low	
Shum et al. 2015 [69]	low	low	high	low	low	low	low	
Siew et al. 2010 [55]	low	low	low	low	unclear	low	high	
Siew et al. 2010 [55] Siew et al. 2013 [56]	low	low	low	low	unclear	low	high	
	11.17/	IL J V V		IUW	unciear	IUVV	110111	

	Patie	nt selection	Inc	Index Test		RRT Initiation	
	Risk of	Applicability	Risk of	Applicability	Risk of	Applicability	Flow &
Author/Year	bias	judgements	bias	judgements	bias	judgements	Timing
Skinner et al. 2017 [81]	low	low	low	low	unclear	low	low
Srisawat et al. 2011 [26]	high	low	unclear	low	unclear	low	low
Sumida et al. 2014 [63]	unclear	low	unclear	low	unclear	low	low
Susantitaphong et al. 2012 [27] Tiranathanagul et al. 2013	low	high	low	low	unclear	low	low
[57]	unclear	low	unclear	low	low	low	low
Valette et al. 2013 [71]	unclear	low	low	low	unclear	low	low

2.2. Supplemental forest plots

Fig. 9 Forest plots of urinary IL-18 predicting RRT. **Fig. 9a** Urinary concentration of IL-18.

Urinary IL-18 (urinary Concentration)

Author(s), Year	Patients	RRT	Weight [%]		AUC [95% CI]
Renhua et al., 2014	103	48	22.4	—	0.600 [0.491, 0.709]
Koyner et al., 2015	77	11	15.9	·•	0.610 [0.473, 0.747]
Nisula et al., 2015	1439	96	31.7	⊢ I	0.655 [0.572, 0.738]
Endre et al., 2011	528	19	16.3	⊢ i	0.730 [0.595, 0.865]
Ralib et al., 2012	481	12	13.7	·	0.800 [0.650, 0.950]
RE Model (Q = 6.04, df = 4, p =	0.20; I ² = 2	26.1%)		•	0.668 [0.606, 0.729]
			0.3 0.4	0.5 0.6 0.7 0.8 0.9	
				AUC (Random effects model)	

Fig. 9b Urinary IL-18 normalized to urinary creatinine.

Urinary IL-18 (normalized to urinary Creatinine)

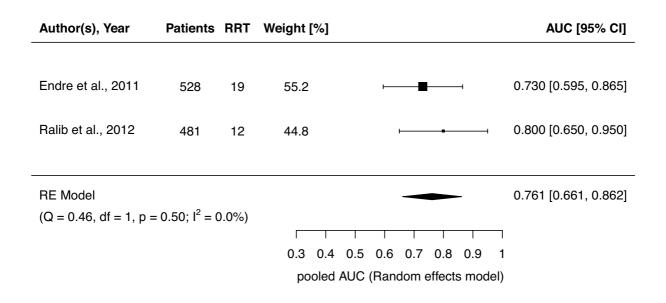


Fig. 10 Forest plots of urinary cystatin C (conc.) predicting RRT Urinary Cystatin C (urinary Concentration)

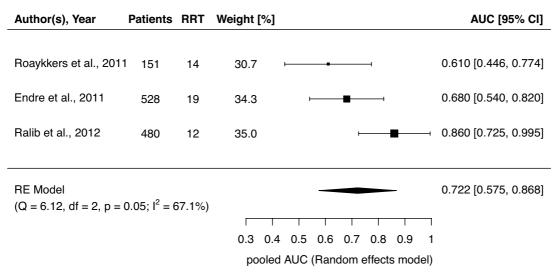


Fig. 11 Forest plots of urinary KIM-1 predicting RRT. **Fig.11a** Urinary concentration of KIM-1.

Urinary KIM-1 (urinary concentration)

Author(s), Year	Patients	RRT	Weight [%]		AUC [95% CI]
Endre et al., 2011	528	19	46.5	⊢∎1	0.550 [0.410, 0.690]
Koyner et al., 2015	77	11	23.7	——	0.610 [0.414, 0.806]
Ralib et al., 2012	481	12	29.8	⊢−−−−− +	0.650 [0.475, 0.825]
RE Model (Q = 0.80, df = 2, p =	$0.67: ^2 = 0$).0%)			0.594 [0.499, 0.689]
()F	,	,			
			0.3	0.4 0.5 0.6 0.7 0.8 0.9	1
			рос	led AUC (Random effects mod	el)

Urinary KIM-1 (normalized to urinary Creatinine)

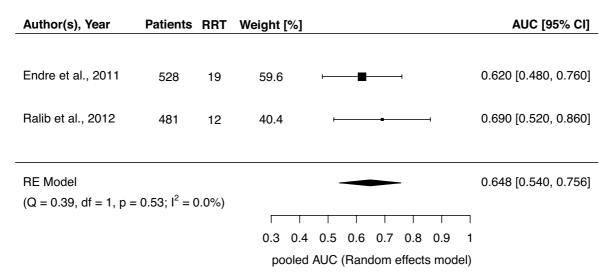
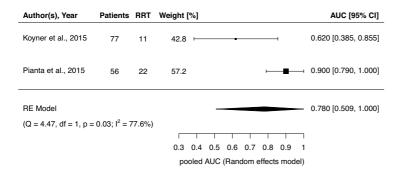


Fig. 12a Forest plot of urinary TIMP-2 predicting RRT. Fig. 12b Forest plot of urinary IGFBP-7 predicting RRT

Urinary TIMP-2

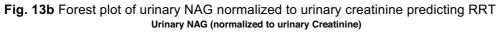


Urinary IGFBP-7

Author(s), Year	Patients	RRT	Weight [%]			AUC [95% CI]
Koyner et al., 2015	77	11	44.0 ⊢			0.570 [0.335, 0.805]
Pianta et al., 2015	56	22	56.0		- 🖬 1	0.830 [0.675, 0.985]
RE Model	0.07.12	CO 40/	、			0.716 [0.463, 0.969]
(Q = 3.27, df = 1, p =	= 0.07;1 =	69.4%	»)			
			0.3 0.4	0.5 0.6 0.7	0.8 0.9 1	
			pooled	AUC (Random et	ffects model)	

Fig. 13a Forest plot of urine output predicting RRT Urine Output

Author(s), Year	Patients	RRT	Weight [%]	AUC [95% CI]
Pickering et al., 2012	484	NA	50.3 ⊢—∎——	0.500 [0.406, 0.594]
Koziolek et al., 2012	120	52	49.7	0.730 [0.630, 0.830]
RE Model				0.614 [0.389, 0.840]
(Q = 10.78, df = 1, p =	0.00; l ² =	90.7%)	
			0.3 0.4 0.5 0.6 0.7 0.8 0.9) 1
			pooled AUC (Random effects mo	dei)



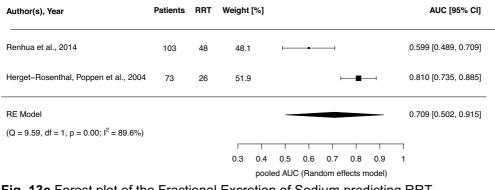
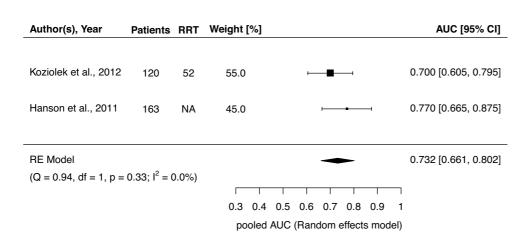


Fig. 13c Forest plot of the Fractional Excretion of Sodium predicting RRT Fractional Excretion of Sodium

Author(s), Year	Patients	RRT	Weight [%]		AUC [95% CI]
Koyner et al., 2015	77	11	29.5	⊢ − − − +	0.640 [0.464, 0.816]
Hanson et al., 2011	163	NA	70.5	⊢− 1	0.750 [0.640, 0.860]
RE Model					0.718 [0.619, 0.816]
(Q = 1.08, df = 1, p =	0.30; I ² = 7	7.0%)			
			0.3 0.4	0.5 0.6 0.7 0.8 0.9 1	
			pooled	AUC (Random effects model)	

Fig. 13d Forest plot of blood urea nitrogen predicting RRT



Blood Urea Nitrogen

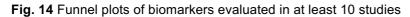


Fig. 14a Funnel plot for the urinary concentration of urinary NGAL

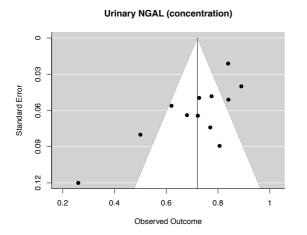


Fig. 14c Funnel plot for plasma and serum creatinine

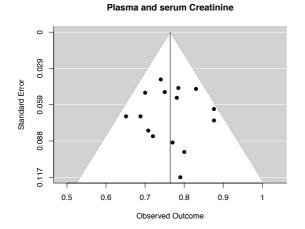
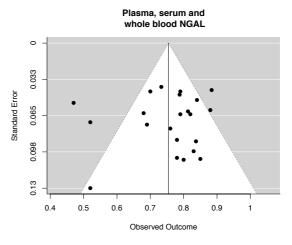


Fig. 14b Funnel plot for plasma, serum and whole blood NGAL



Tab. 3 Differences between pooled AUCs for urinary biomarkers

	IL-18	Cystatin C	KIM-1
	urinary conc. vs. normalized to urinary	urinary conc. vs. normalized to urinary	urinary conc. vs. normalized to urinary
	creatinine	creatinine	creatinine
Difference	0.007	0.068	0.054
p-value	0.8863	0.5172	0.4618

Tab. 4 Differences between pooled AUCs for NGAL

	NGAL plasma vs. serum	blood NGAL vs. urinary NGAL (concentration)	blood NGAL vs. urinary NGAL (normalized)
Difference	0.114	0.035	0.028
p-value	0.1593	0.4735	0.4260

Tab. 5 Differences between pooled AUCs for blood creatinine and cystatin C

	Creatinine plasma vs. serum	Cystatin C plasma vs. serum	p+s Cystatin C vs. urinary CysC (concentration)	p+s Cystatin C vs. urinary CysC (normalized)
Difference	0.013	0.077	0.046	0.022
p-value	0.7178	0.3310	0.5520	0.7733

3. Sensitivity analyses

3.1. Inclusion of moderators into the Random Effects Model

To address the between-trial heterogeneity, moderators (number of patients receiving RRT) were added to the random-effects model on an exploratory basis, but no significant findings were noticed during this process.

For *plasma/serum/whole blood NGAL*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=69.18 (df=21) to Q=69.1 (df=20). The effect of the incidence of RRT is not statistical significant: Q=0.02 (df=1). For *plasma/serum creatinine*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=15.23 (df=14) to Q=8.83 (df=9). The effect of the incidence of RRT is not statistical significant: Q=0.07 (df=1).

For *plasma/serum cystatin C*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=4.9 (df=6) to Q=2.75 (df=4). The effect of the incidence of RRT is not statistical significant: Q=0.01 (df=1).

For *urinary TIMP-2*IGFBP-7*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q= 5.7 (df=3) to Q=5.66 (df=2). The effect of the incidence of RRT is not statistical significant: Q=0.00 (df=1).

For *urinary cystatin C (conc.)*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=6.12 (df=2) to Q=4.02 (df=1). The effect of the incidence of RRT is not statistical significant: Q=0.38 (df=1).

For *urinary cystatin C (norm.)*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=19.70 (df=3) to Q=11.62 (df=2). The effect of the incidence of RRT is not statistical significant: Q=0.48 (df=1).

For *urinary NGAL (conc.)*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=60.25 (df=11) to Q=45.58 (df=9). The effect of the incidence of RRT is not statistical significant: Q=1.45 (df=1).

For *urinary NGAL (norm.)*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=12.94 (df=6) to Q=12.84 (df=5). The effect of the incidence of RRT is not statistical significant: Q=0.14 (df=1).

For *urinary IL-18 (conc.)*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=6.04 (df=4) to Q=5.44 (df=3). The effect of the incidence of RRT is not statistical significant: Q=0.41 (df=1).

For *urinary KIM-1 (conc.)*, the test for residual heterogeneity and for moderators shows no significant influence of the incidence of RRT. The residual heterogeneity decreases from Q=0.80 (df=2) to Q=0.14 (df=1). The effect of the incidence of RRT is not statistical significant: Q=0.65 (df=1).

It was not possible to add moderators to the RE models of BUN, FeNa, TIMP-2, IL-18 (norm.), IGFBP-7, NAG, KIM-1 (norm.) and UO due to the limited number of studies included in these RE models.

3.2. Paired analysis of biomarkers reported in the same study

Another process applied to address between-trial heterogeneity was to pair biomarkers reported in the same studies and create an estimate of the average AUC improvement for those biomarkers.

When comparing plasma, serum and whole blood NGAL and plasma/serum creatinine in studies that provide results for both biomarkers, the performance of NGAL is slightly better than creatinine (AUC improvement Hjortrup -0.04, Valette +0.04, Pickering +0.07, Tiranathanagul +0.10, Sumida +0.06, Maisel +0.01, Gaipov -0.13, Mahdavi-Mazdeh +0.00, average AUC improvement 0.013) as opposed to the pooled AUC from the unpaired analysis.

The trend for plasma/serum cystatin C of outperforming plasma/serum creatinine still holds true after pairing those biomarkers (Nejat +0.07, Koziolek +0.04, Pipili -0.02, Renhua -0.013, Kiessling -0.03, average AUC improvement 0.01).

Urinary TIMP-2 which is outperformed by TIMP-2*IGFBP-7 in the pooled analysis, shows improved performance, indicating a slightly better predictive performance than TIMP-2 and IGFBP-7 combined, when only comparing the reported values by Koyner and Pianta (AUC improvement +0.01 and +0.02, respectively, average AUC improvement 0.015).

Urinary cystatin C (conc.) outperforms urinary IL-18 (conc.) in the pooled analysis, this gap diminishes when pairing those biomarkers (AUC improvement for Endre and Ralib -0.05 and +0.06, respectively, average AUC improvement 0.005). When urinary cystatin C and IL-18 were normalized to urinary creatinine, cystatin C still performs slightly better than IL-18 (AUC improvement -0.02, +0.08, respectively, average AUC improvement 0.03).

For urinary NGAL (norm.), which is outperformed by urinary cystatin C (norm.), a slight improvement can be noted when pairing it with cystatin C (norm.) (AUC improvement Endre +0.08, Ralib -0.04, average AUC improvement 0.02; note: only 2 of 7 studies for urinary NGAL considered for paired analysis, omitting 5 studies).

While urinary NGAL (norm.) is outperformed by urinary IL-18 (norm.) the opposite holds true for NGAL (conc.) and IL-18 (conc.). When pairing NGAL (conc.) and IL-18 (conc.), NGAL slightly outperforms IL-18 (AUC improvement Renhua +0.17, Koyner -0.11, Endre +0.04, average AUC improvement 0.035), while IL-18 (norm.) is slightly better than NGAL (norm.) (AUC improvement Endre +0.06, Ralib +0.04, average AUC improvement 0.05).

3.3. Subgroup analysis for biomarkers included in the meta-analysis

Tab. 6 Subgroup analysis for plasma, serum and whole blood NGAL. Mixed ICU populations are ICU cohorts which include medical and surgical patients. Excluded from this category are studies only investigating specific patient cohorts for example after cardiac surgery, after renal transplantation, suffering from malaria etc. Difference means difference between pooled AUCs

	p/s/wb NGAL (all studies)	mixed ICU populations only	cut-off 150- 350 ng/ml	cut-off >600 ng/ml	cut-off 150- 350 vs. >600 ng/ml
AUC	0.755	0.747	0.742	0.779	
(95%-CI)	(0.706-0.803)	(0.685-0.808)	(0.678-0.805)	(0.689-0.870)	
Difference		0.008	0.013	0.024	0.037
p-value		0.8413	0.7964	0.6469	0.5613

Fig. 15 Plasma, serum and whole blood NGAL. Subgroup analysis including only mixed ICU	
populations	

Plasma, serum and whole blood NGAL Mixed ICU population only

AUC [95% CI]		Weight [%]	RRT	Patients	Author(s), Year
0.470 [0.365, 0.575]	⊧ ∎ i	8.4	11	140	Royakkers et al., 2012
0.520 [0.265, 0.775]	·	3.8	11	77	Koyner et al., 2015
0.680 [0.557, 0.803]	⊢	7.7	24	227	Rewa et al., 2015
0.700 [0.615, 0.785]	F	9.1	40	222	Hjortrup et al., 2015
0.733 [0.656, 0.810]	⊢	9.4	47	369	Linko et al., 2013
	⊢	6.0	13	83	Bagshaw et al., 2010
. 0.780 [0.579, 0.981]	⊢	5.0	7	102	Glassford et al., 2013
⊢−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−	⊢≣	8.9	7	88	Constantin et al., 2010
⊢−−−− − −−−− 0.790 [0.665, 0.915]	⊢	7.6	45	528	Pickering et al., 2013
∟−−−−− 0.813 [0.693, 0.933]	⊢	7.8	18	47	Tiranathanagul et al., 2013
⊢−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−	⊢∎	7.6	15	301	Cruz et al., 2009
⊢−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−	⊢	5.9	7	151	Shum et al., 2015
⊢ 0.850 [0.647, 1.000]		5.0	6	31	Sumida et al., 2014
⊢−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−	⊢ ∎	7.9	28	632	de Geus et al., 2011

0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1 pooled AUC (Random effects model)

 $(Q = 42.89, df = 13, p = 0.00; l^2 = 70.0\%)$

Fig. 16 Subgroup analysis for different NGAL thresholds

Fig. 16a Plasma, serum and whole blood NGAL. Subgroup analysis including only studies with stated cut-off between 150 and 350 ng/ml

Author(s), Year	Patients	RRT	Weight [%]		AUC [95% CI]
Gaipov et al., 2015	60	7	11.4		0.520 [0.381, 0.659]
Chun et al., 2017	76	20	11.1	⊢	0.690 [0.547, 0.833]
Linko et al., 2013	369	47	18.3	⊢∎1	0.733 [0.656, 0.810]
Lukasz et al., 2014	39	24	10.5	⊢ I	0.760 [0.610, 0.910]
Constantin et al., 2010	88	7	16.6	⊢	0.788 [0.698, 0.878]
Valette et al., 2013	98	6	17.3	⊢∎ 1	0.790 [0.705, 0.875]
Haase-Fielitz et al., 2009	100	4	7.8	·•	0.830 [0.640, 1.000]
Sumida et al., 2014	31	6	7.1	·	0.850 [0.647, 1.000]
RE Model ($\Omega = 1450$, df = 7, n = 0.04: l^2 =	54 6%)				0.742 [0.678, 0.805]

Plasma, serum and whole blood NGAL Cut-off 150-350 ng/ml

(Q = 14.50, df = 7, p = 0.04; l² = 54.6%)

0.3 0.4 0.5 0.6 0.7 0.8 0.9 pooled AUC (Random effects model)

1

Fig. 16b Plasma, serum and whole blood NGAL. Subgroup analysis including studies with stated cutoff ≥600 ng/ml

Plasma, serum and whole blood NGAL Cut-off >600 ng/ml

Author(s), Year	Patients	RRT	Weight [%]		AUC [95% CI]
Hjortrup et al., 2015	222	40	37.9	⊢	0.700 [0.615, 0.785]
Tiranathanagul et al., 2013	47	18	28.5	⊢	0.813 [0.693, 0.933]
Cemil et al., 2014	60	30	33.6		0.840 [0.740, 0.940]
			0010		

0.779 [0.689, 0.870]

(Q = 4.98, df = 2, p = 0.08; l² = 58.7%)

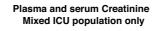
RE Model

0.5 0.6 0.7 0.8 0.9 1 pooled AUC (Random effects model)

	p/s Cr	mixed ICU
	(all studies)	populations
		only
AUC	0.764	0.736
(95%-CI)	(0.732-0.796)	(0.694-0.777)
Difference		0.028
p-value		0.2950

Tab. 7 Subgroup analysis for plasma and serum creatinine. Differences between pooled AUCs

Fig. 17 Plasma and serum creatinine.	e. Subgroup analysis including only mixed ICU populations
--------------------------------------	---



Author(s), Year	Patients	RRT	Weight [%]		AUC [95% CI]
Drey et al., 2015	61	NA	9.7	·	0.688 [0.555, 0.821]
Koziolek et al., 2012	120	52	18.7	⊢ i	0.700 [0.604, 0.796]
Tiranathanagul et al., 2013	47	18	7.1	⊢	0.708 [0.552, 0.864]
Pickering et al., 2012	484	NA	6.3	⊢	0.720 [0.555, 0.885]
Hjortrup et al., 2015	222	40	30.6	⊢∎ i	0.740 [0.665, 0.815]
Nejat et al., 2010	444	14	5.6	⊢−−−− −−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−	0.770 [0.595, 0.945]
Pipili et al., 2014	106	50	22.0	F1	0.785 [0.696, 0.874]
RE Model (Q = 2.53, df = 6, p = 0.87; l ² = 0.	0%)			•	0.736 [0.694, 0.777]
			۲ ٥.	4 0.5 0.6 0.7 0.8 0.9 1 pooled AUC (Random effects model)	

Tab. 8 Subgroup analysis for plasma and serum Cystatin C. Differences between pooled AUCs

	p/s CysC	mixed ICU
	(all studies)	populations
		only
AUC	0.768	0.755
(95%-CI)	(0.729-0.807)	(0.710-0.801)
Difference		0.013
p-value		0.6706

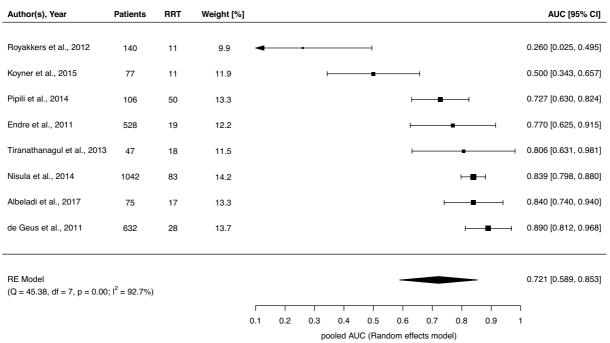
Fig. 18 Plasma and serum Cystatin C. Subgroup analysis including only mixed ICU populations Plasma and serum Cystatin C Mixed ICU population only

Author(s), Year	Patients	RRT	Weight [%]		AUC [95% CI]
Royakkers et al., 2011	151	14	8.0	·	0.660 [0.498, 0.822]
Koziolek et al., 2012	120	52	25.1	⊢	0.740 [0.649, 0.831]
Herget-Rosenthal et al., 2004	85	17	32.8	⊢∎ 1	0.760 [0.680, 0.840]
Pipili et al., 2014	106	50	24.8	⊢ +	0.764 [0.672, 0.856]
Nejat et al., 2010	444	14	9.3	 i	0.840 [0.690, 0.990]
					0.755 [0.710, 0.901]
$(Q = 2.71, df = 4, p = 0.61; l^2 = 0.01)$	10/)			•	0.755 [0.710, 0.801]
$(\alpha = 2.71, \alpha = 4, \beta = 0.01, 1 = 0.0$	776)		F		
			0.4	0.5 0.6 0.7 0.8 0.9 1	
				pooled AUC (Random effects model)	

Tab. 9 Subgroup analysis for urinary NGAL (concentration and normalized to urinary creatinine). Differences between pooled AUCs

	urinary NGAL	mixed ICU	urinary NGAL	mixed ICU
	(concentration)	populations	(normalized)	populations
	(all studies)	only	(all studies)	only
AUC	0.720	0.721	0.727	0.710
(95%-CI)	(0.638-0.803)	(0.589-0.853)	(0.678-0.776)	(0.605-0.815)
Difference		0.001		0.017
p-value		0.9900		0.7737

Fig. 19 Subgroup analysis for urinary NGAL (conc.) including only mixed ICU populations Fig. 19a Subgroup analysis including only mixed ICU populations for the urinary concentration of urinary NGAL



Urinary NGAL (urinary concentration) Mixed ICU population only

Fig. 19b Subgroup analysis including only mixed ICU populations for urinary NGAL normalized to urinary creatinine

Urinary NGAL (normalized to urinary Creatinine) Mixed ICU population only

Author(s), Year	Patients	RRT	Weight [%]	AU	C [95% CI]
Royakkers et al., 2012	140	11	9.1 ┥		000, 0.555]
Bagshaw et al., 2010	83	13	20.3	⊢ ■ 0.700 [0.4	580, 0.820]
Glassford et al., 2013	102	7	12.8	⊢−−−−− −−−−−−−−−−−−−−−−−−−−−−−−−−−−−−−	490, 0.920]
Pipili et al., 2014	106	50	22.5	⊢∎1 0.737 [0.	641, 0.833]
Endre et al., 2011	528	19	18.1	⊢ 0.790 [0.	645, 0.935]
Ralib et al., 2012	449	10	17.2	⊢I 0.840 [0.6	685, 0.995]
RE Model				0.710 [0.6	605, 0.815]
(Q = 12.91, df = 5, p = 0.02	2; I ² = 64.8%)				
			0.1 0.2	2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1	
				pooled AUC (Random effects model)	