Published in final edited form as:

Am J Kidney Dis. 2013 March ; 61(3): 430–439. doi:10.1053/j.ajkd.2012.10.016.

Performance of Urinary Liver-Type Fatty Acid–Binding Protein in Acute Kidney Injury: A Meta-analysis

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Abstract

Background—Urinary liver-type fatty acid-binding protein (L-FABP) is a proximal tubular injury candidate biomarker for early detection of acute kidney injury (AKI), with variable performance characteristics depending on clinical settings.

Study Design—Meta-analysis of diagnostic test studies assessing the performance of urinary L-FABP in AKI.

Setting & Population—Literature search in MEDLINE, EMBASE, Scopus, Google Scholar, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov using search terms “liver-type fatty acid-binding protein” and “L-FABP”.

Selection Criteria for Studies—Human studies investigating the performance characteristics of urinary L-FABP for early diagnosis of AKI and AKI-related outcomes, including dialysis requirement and mortality.

Predictor—Urinary L-FABP.

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SECTION: Because an author of this manuscript is an editor for AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Emmanuel A. Burdmann, MD, PhD) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Editorial Policies section of the AJKD website.

The remaining authors declare that they have no other relevant financial interests.

Supplementary Material

Table S1: Methodological quality of the 21 studies included in the meta-analysis. *Note:* The supplementary material accompanying this article (doi: _____) is available at www.ajkd.org

Descriptive Text for Online Delivery

Hyperlink: Supplementary Table S1 (PDF)

About: Methodological quality of the 21 studies included in the meta-analysis.

Outcomes—Diagnosis of AKI, dialysis requirement, and in-hospital death.

Results—15 prospective cohort studies and 2 case-control studies were identified. Only 7 cohort studies could be meta-analyzed. The estimated sensitivity of urinary L-FABP for diagnosis of AKI was 74.5% (95% CI, 60.4-84.8), and the specificity was 77.6% (95% CI, 61.5-88.2). The estimated sensitivity of urinary L-FABP for predicting dialysis requirement was 69.1% (95% CI, 34.6-90.5), and the specificity was 42.7% (95% CI, 3.1-94.5); for in-hospital mortality, sensitivity and specificity were 93.2% (95% CI, 66.2-99.0) and 78.8% (95% CI, 27.0-97.4), respectively.

Limitations—Paucity and low quality of studies, different clinical settings, and variable definitions of AKI.

Conclusions—Although urinary L-FABP may be a promising biomarker for early diagnosis of AKI, and for predicting dialysis requirement and in-hospital mortality, its potential value needs to be validated in large studies and across a broader spectrum of clinical settings.

Keywords

L-FABP; biomarker; AKI; systematic review; meta-analysis

Despite recent advances in the development of a serum creatinine-based consensus definition and staging of acute kidney injury (AKI)^{1,2}, this serious and common hospital-associated condition^{3,4} confers an increased in-hospital mortality risk, prolonged hospital length of stay, higher hospital-associated healthcare expenditures⁵⁻⁷, and a subsequent long-term risk of development of chronic kidney disease, kidney failure and death⁸⁻¹⁰. A possible barrier to improving clinical outcomes in patients with AKI might be due in part to potentially beneficial therapies not being given to patients quickly enough^{11,12}, especially in light of the unreliability of serum creatinine as a marker of glomerular filtration in acutely ill patients^{13,14}. As a result, in recent years, efforts directed toward the development of novel markers for early detection and prognostication of AKI have yielded several candidate molecules, with variable performance¹⁵⁻¹⁸.

Liver-type fatty acid-binding protein (L-FABP), one such candidate biomarker, is a 14 kDa protein expressed in the proximal tubular epithelial cells¹⁹. This endogenous antioxidant promotes free fatty acid metabolism by binding long-chain fatty acid oxidation products²⁰. The L-FABP gene is responsive to a hypoxic stress, which occurs in the setting of kidney ischemia-reperfusion injury. As a consequence, the urinary excretion of L-FABP reflects stress of proximal tubular epithelial cells, correlating with severity of ischemic tubular injury²¹⁻²⁵. The performance of urinary L-FABP as an early detection marker of AKI has shown promise in various clinical settings²⁶⁻³¹. However, there remains skepticism as to whether urinary biomarkers will provide reliable diagnostic and prognostic stratification to assist physicians in the early management of AKI³². To systematically assess the performance characteristics of urinary L-FABP as a potentially suitable marker for early diagnosis and prognosis of AKI, we conducted a meta-analysis of all observational studies that have tested this biomarker in the setting of AKI.

METHODS

Data Sources and Searches

We performed a MEDLINE literature search (from inception to September 24, 2012) to identify eligible studies using the search terms “liver-type fatty acid-binding protein” or “L-FABP”. The search was limited to human studies. We also searched EMBASE, Scopus, and Google Scholar, as well as the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov for completed studies using similar search terms. We also reviewed the

American Society of Nephrology abstracts (2003-2011 meetings) and the bibliographies of retrieved articles.

Study Selection

We included case-control and prospective cohort studies of humans investigating the performance characteristics of urinary L-FABP for the diagnosis of AKI, and for AKI-related outcomes, including dialysis requirement, recovery of kidney function, or in-hospital mortality. If more than one publication appeared in the same study, data from the most inclusive report were used. There were no language or sample size restrictions. Non-English citations and full-text articles were scanned using Google Translate. Two authors (PS, MS) initially screened the titles and abstracts of all the electronic citations using the EndNote bibliography manager (EndNote X4; Thomson Reuters), and then retrieved and re-screened full-text articles. We hand searched the bibliography of retrieved articles for additional relevant studies. Non-peer reviewed scientific abstracts were searched electronically in the abstract CD-ROMs of the annual meetings of the *American Society of Nephrology*.

Data Extraction and Quality Assessment

The data were extracted by three of the authors (PS, MS, and KD). A third author (BLJ) settled disagreements through consensus and arbitration. Corresponding authors of 4 trials were contacted by e-mail for data clarification, 2 of whom provided additional information^{25,33}.

Data extraction included country of origin, year of publication, study design, sample size, clinical setting (e.g., cardiopulmonary bypass surgery, cardiac catheterization, critical care, general hospital ward, and emergency ward), and patient characteristics (age, sex, and baseline serum creatinine). The definition of AKI and number of patients who developed AKI, initiated dialysis, recovered kidney function, and died in-hospital were also recorded. Data extraction regarding L-FABP included the laboratory assay used, the reported biomarker value unit (nanograms per milliliter *vs.* nanograms per milligram of creatinine), and the timing of the measurement; for the outcomes of interest, the optimal cut-off thresholds, as defined by the authors of the individual studies, and the true-positive, true-negative, false-positive, and false-negative values were included.

The quality of the individual studies examining the performance of urinary L-FABP for diagnosis of AKI was assessed by 2 authors (PS, MS) independently, using the QUALity Assessment of Diagnostic Accuracy Studies (QUADAS) tool³⁴. This tool assesses the validity of diagnostic accuracy studies, and comprises 14 methodological items phrased as questions (each of which scored as a “yes”, “no” or “unclear”) that assess bias in the study³⁵. Inter-rater agreement for the final selection of the articles and for quality assessment was evaluated using the kappa coefficient.

Data Synthesis and Analysis

We performed bivariate-model meta-analysis of the prospective cohort studies with adequate data to calculate a hierarchical summary area under the receiver operating characteristic (ROC) curve as well as estimated sensitivities and specificities for diagnosis of AKI³⁶. Whenever the bivariate models were not applicable due to small sample size, random-effects model meta-analyses were used to compute estimated sensitivities, specificities, and diagnostic odds ratios (DORs) with a 95% confidence interval (CI) for the outcomes of dialysis requirement and in-hospital death. Heterogeneity was assessed using the I^2 index and the Q test P value. For these analyses, we used the *optimal* L-FABP cut-off point value (i.e., the value that is closest to the left upper corner of the ROC curve) reported

in individual studies that predicted the outcomes of interest¹⁸. The timing of L-FABP measurement in relation to the development of AKI was also considered in some of the clinical settings. The analyses were performed using OpenMeta[Analyst].^{36a}

RESULTS

Study Characteristics

A total of 6,691 potentially relevant citations were identified and screened; 100 articles were evaluated in detail, of which 23 met eligibility criteria (3,415 patients; Figure 1)^{25,33,37-57}. The inter-rater agreement kappa coefficient for the final selection of the included articles was 0.94. Characteristics of the individual studies are displayed in Table 1. There were 21 prospective cohort studies^{25,33,37-40,42,43,45-57} and 2 cross sectional studies^{41,44}. Seventeen studies were peer-reviewed publications^{25,33,37-39,41-44,47,48,52-57} and six were published in abstract format^{40,45,46,49-51}. All studies enrolled adults with the exception of 2 studies that enrolled children^{38,48}. The studies were published over approximately 5 years, varied in sample size (20-1,212 patients) and involved patients in different clinical settings, including cardiopulmonary bypass surgery (635 patients), cardiac catheterization (609 patients), critical illness (605 patients), emergency ward (1,212 patients), general hospital ward (290 patients), liver transplantation (25 patients), and hematopoietic stem cell transplantation (39 patients). The mean age ranged from 47 to 73 years in studies of adults and 2.6 to 3.5 years in studies of children. All studies measured L-FABP in urine, and two studies measured the biomarker in plasma^{38,41}. All studies used a commercial enzyme-linked immunosorbent assay to measure L-FABP.

Quality Assessment

All studies employed a convenience sample, and blinding of investigators was documented in only 3 studies^{38,48,54}. The potential role of the assay's manufacturer in the funding of the studies was not reported in any of the studies. Among the 11 studies that reported on sample storage, urine was stored at -80°C ^{25,33,38,40,44,47,48,53-55,57}. As shown in Table 1, variable definitions of AKI were adopted in the individual studies.

The methodological quality of the studies according to the QUADAS tool is summarized in Table S1 (provided as online supplementary material). The kappa coefficient for assessing study quality was 0.65. Overall, the quality of the studies was suboptimal with insufficient information to assess bias. The index and reference tests were not described in sufficient detail to permit their replication. The index test results were interpreted with knowledge of the results of the reference standard for the clinical diagnosis of AKI (based on serum creatinine), and uninterpretable indeterminate, or intermediate index test results were not reported.

Data Synthesis

Table 2 displays the optimal cut-off point values of urinary L-FABP identified in the individual studies representing various clinical settings of AKI. It also shows the true-positive, false-positive, false-negative, and true-negative values, sensitivities, specificities, and ROC curves for diagnosis of AKI, dialysis requirement, recovery of kidney function, and mortality.

Of the 12 prospective cohort studies that reported on diagnosis of AKI, only 7^{33,38,47,53,55-57} could be meta-analyzed, as the remaining reports did not provide the required numerical data^{48-50,52,54}. The estimated sensitivity of urinary L-FABP for diagnosis of AKI was 74.5% (95% CI, 60.4-84.8), and the specificity was 77.6% (95% CI, 61.5-88.2), with a DOR of 2.69 (95% CI, 1.63-4.43; $P<0.001$). There was moderate

heterogeneity between studies as evidenced by an I^2 index of 41% and a Q test P value of 0.1. The hierarchical summary ROC curve is shown in Figure 2.

Four studies reported on the incidence of dialysis requirement^{33,40,46,53}, one study on recovery of kidney function⁵⁰, and 5 studies on mortality^{25,33,49,50,53}. Dialysis was required in 8%-43% of patients, and mortality ranged from 4%-47%. The performance characteristics of L-FABP for prediction of dialysis requirement could only be meta-analyzed in 3 of 4 studies^{33,40,53}, as one study lacked the required data⁴⁶. For predicting dialysis requirement, the estimated sensitivity of urinary L-FABP was 69.1% (95% CI, 34.6-90.5) and the specificity was 42.7% (95% CI, 3.1-94.5), with a DOR of 2.24 (95% CI, 0.53-9.50; $P=0.3$). There was moderate heterogeneity between studies as evidenced by an I^2 index of 36% and a Q test P value of 0.2.

In the one study that reported on recovery of kidney function at the time of hospital discharge⁵⁰, post-operative urinary L-FABP displayed good discrimination for predicting non-recovery of kidney function with an area under the curve of 0.775⁵⁰. However, the definition of this outcome was not specified.

Of the 5 studies that reported on mortality, only 3 could be meta-analyzed^{25,33,53} as the remaining 2 studies lacked the required data^{49,50}. In brief, for predicting mortality, the estimated sensitivity of urinary L-FABP was 93.2% (95% CI, 66.2-99.0) and the specificity was 78.8% (95% CI, 27.0-97.4), with a DOR of 13.72 (95% CI, 1.96-95.89; $P=0.008$). There was moderate heterogeneity (I^2 index = 51%; Q test $P=0.1$; Table 3).

DISCUSSION

Research efforts to discover novel urinary biomarkers that enhance the ability to predict both development and evolution of AKI, with the hope that such advances might facilitate timely introduction of AKI-specific therapies, are underway. In the present systematic review, we summarize the results of all the published studies that have examined the performance characteristics of one such urinary biomarker, L-FABP. Of the 12 identified cohort studies of patients at-risk for AKI, only 7 could be meta-analyzed for diagnosis of AKI, whereby urinary L-FABP displayed good performance characteristics with high sensitivity and specificity, especially among patients undergoing cardiac surgery at risk for development of AKI. Fewer studies could be analyzed for the outcomes of dialysis and in-hospital mortality. Overall, the results provide some support for the use of this promising biomarker in AKI.

In 2005, the American Society of Nephrology recognized that the identification and characterization of biomarkers for early detection and prognostication of AKI should be a research focus of highest priority⁵⁸. As a result, several promising urinary biomarkers for early detection of AKI have emerged in the literature, including neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1)^{18,26,31}. Liver-type Fatty Acid-Binding Protein is a 14 kDa protein that is expressed in proximal tubular epithelial cells. Its urinary appearance correlates with the extent of ischemia-reperfusion injury in experimental models of AKI²⁴, and with cold ischemic time in kidney transplant recipients⁵⁹. Although the performance of urinary L-FABP as an early detection marker of AKI has shown some promise in various clinical settings²⁶⁻³¹, in our analysis of the existing data, this biomarker displayed good performance. Although, urinary L-FABP has also been shown to correlate with fibrotic changes in experimental models of chronic kidney disease²³, due to scant data, we were unable to formally assess the performance of this biomarker for predicting non-recovery of kidney function in patients with AKI.

Neutrophil gelatinase-associated lipocalin, another proximal tubular injury marker that is upregulated in response to ischemic and nephrotoxic insults⁶⁰, remains the most studied and

best characterized biomarker in AKI. In a prior meta-analysis of 19 studies involving 2,538 patients, urinary NGAL displayed excellent performance for prediction of AKI, as evidenced by a summary ROC curve of 0.837 (95% CI, 0.762-0.906).¹⁸ The performance of NGAL was more robust following radiocontrast exposure and cardiac surgery, and in studies of children rather than adults. We were unable to explore similar subgroup analyses due to the small number of studies identified.

The main strength of our systematic review is that it appears to be the first analysis of all published cohort studies of patients at-risk for AKI (3,415 analyzable patients) that summarizes the diagnostic and prognostic performance of urinary L-FABP. Limitations of the analysis include the small number of studies, the low quality of the studies according to the QUADAS tool, the heterogeneity in study populations with a broad range of clinical settings, the variable definitions of AKI (reference standard test), the variable biomarker cut-off values (index test), and the variable duration of follow up. The wide confidence intervals of the DORs, along with the aforementioned sources of heterogeneity of the few included studies, render the results difficult to interpret.

In our analysis, urinary L-FABP did not perform as well for predicting dialysis requirement as for detecting AKI or mortality. We can only speculate as to whether dialysis requirement as a clinical endpoint is confounded by clinical practice pattern variations that dictate dialysis initiation and survival bias—2 important factors that might affect the performance characteristic of any biomarker for predicting this outcome as compared to other more finite endpoints such as development of AKI and mortality. We also had fewer studies to ascertain dialysis requirement as a clinical endpoint, which likely affected the summary estimates.

We were unable to formally assess non-AKI related factors that might influence urinary L-FABP, such as sepsis and preexisting chronic kidney disease, due to the small number of studies and the exclusion of patients with pre-existing kidney disease in most of the reports. There is published work suggesting that circulating (not urinary) L-FABP is a marker of liver injury in critically ill patients with sepsis⁶¹. Urinary L-FABP has also been shown to be of some value in predicting progression of chronic kidney disease⁶², and in predicting pharmacological response to blockade of the renin angiotensin aldosterone system in patients with type-2 diabetes mellitus and proteinuria⁶³. Although sepsis is likely to influence all biomarkers of kidney injury, we were unable to formally assess the impact of sepsis on the performance of L-FABP in the setting of sepsis. From our analysis, we are also unable to formally define when urinary L-FABP should be measured for early detection of AKI or for predicting the prognosis of AKI. These optimal time points are likely dependent on the clinical setting. In our subgroup analysis of patients undergoing cardiac surgery, the 4-hour post-operative time-point offered good biomarker performance. Most studies on the potential value of urinary biomarkers for early detection, differential diagnosis, and prognostication are unable to decipher whether single or multiple measurements are required to improve performance characteristics of the marker under study^{13,16,64,65}, and L-FABP is no exception. Finally, although our analysis examined the value of urinary L-FABP as a predictor of adverse outcomes, we were unable to assess whether this marker adds value to other clinical factors or to a panel of urinary markers of kidney injury^{13,64}, which is an important limitation.

In conclusion, the present meta-analysis demonstrates that in hospital-based cohorts of patients at-risk for AKI, urinary measurement of L-FABP, a proximal tubular injury marker, provides good discrimination for diagnosis of AKI and prediction of dialysis requirement and in-hospital mortality. The potential diagnostic and prognostic value of this biomarker needs to be further validated in large cohort studies, and across a broad spectrum of clinical settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: This work was made possible in part through Dr Susantitaphong's International Society of Nephrology-funded Fellowship. This work was supported in part by grant UL1 RR025752 from the National Center for Research Resources (NCRR). The content does not necessarily represent the official views of the NCRR or the National Institutes of Health.

Financial Disclosure: Dr Jaber has received research funding from Argutus Medical Ltd.

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Figure 1.
Study selection flow diagram.

Figure 2. Hierarchical summary receiver operating characteristic curve displaying the performance of urinary liver-type fatty acid-binding protein for the early diagnosis of acute kidney injury (across all clinical settings).

Table 1

Characteristics of the studies included in the systematic review

Study	Country	N	Patients with AKI***	Population settings	Age (y)	Males (%)	Baseline SCr (mg/dL)**	Definition of AKI	Blinding of investigators	Sample storage
Nakamura et al, ³⁷ 2006	Japan	96	13 (19.7)	Cardiac catheterization	60	70	1.58	>25% or >0.5 mg/dL increase in SCr within 2-5 d	NR	NR
Portilla et al, ³⁸ 2008	USA	40	21 (52.5%)	CPB surgery	4	53	0.46	50% increase in SCr	Yes	-80°C
Kato et al, ³⁹ 2008	Japan	87	18 (20.7%)	Cardiac catheterization	67	71	1.00	>25% or >0.5 mg/dL increase in SCr within 48 h	NR	NR
Hamasaki et al, ⁴⁰ 2008 *	Japan	20	20 (100%)	General hospital ward	66	80	NR	RIFLE criteria	NR	-80°C
Nakamura et al, ⁴¹ 2009	Japan	110	20	General hospital ward	57	71	<1.20	NR [†]	NR	NR
Bachorzewska-Gajewska et al, ⁴² 2009	Poland	25	0 (0%)	Cardiac catheterization	64	NA	0.94	>25% increase in SCr within 48 h	NR	NR
Malyszko et al, ⁴³ 2009	Poland	140	16 (11.4%)	Cardiac catheterization	64	NA	1.02	>25% increase in SCr within 48 h	NR	NR
Ferguson et al, ⁴⁴ 2010	USA	160	92 (57.5%)	General hospital ward; critical care setting; cardiac catheterization	58	56	NR	50% increase in SCr	NR	-80°C
Doi et al, ²⁵ 2010	Japan	145	145 (100%)	Critical care setting	65	59	<1.20	RIFLE criteria	NR	-80°C
Morito et al, ⁴⁵ 2010 *	Japan	39	18 (46.2%)	Hematopoietic stem cell transplantation	48	NA	NR	RIFLE criteria	NR	NR
Arthur et al, ⁴⁶ 2010 *	USA	NA	117	CBP surgery	NR	NA	NR	AKIN criteria	NR	NR
Nozue et al, ⁵⁶ 2010	Japan	96	5 (5.2%)	Cardiac catheterization	70	76	1.00	>25% or >0.5 mg/dL increase in SCr within 72 h	NR	NR
Doi et al, ³³ 2011	Japan	339	131 (39%)	Critical care setting	66	65.8	0.82	RIFLE criteria	NR	-80°C
Matsui et al, ⁴⁷ 2011	Japan	25	14 (56%)	Critical care setting	73	60	0.60	0.3 mg/dL or 50% increase in SCr	NR	-80°C
Krawczeski et al, ⁴⁸ 2011	USA	220	60 (27%)	CPB surgery	3	50	0.37	50% increase in SCr within 48 h	Yes	-80°C

Study	Country	N	Patients with AKI ^{****}	Population settings	Age (y)	Males (%)	Baseline SCr ^{***} (mg/dL)	Definition of AKI	Blinding of investigator ^s	Sample storage
Cho et al, ⁴⁹ 2011 [*]	Korea	96	35 (36.5%)	Critical care setting	NR	NA	NR	NA	NR	NR
Shang et al, ⁵⁰ 2011 [*]	China	NA	NA	CPB surgery	NR	NA	NR	AKIN criteria	NR	NR
Inoue et al, ⁵¹ 2011 [*]	Japan	41	14 (34%)	Cardiac catheterization (stage-3 CKD)	NR	NA	NR	>10 mL/min/1.73 m ² decrease in eGFR	NR	NR
Manabe et al, ⁵² 2012	Japan	22 0	19 (8.6%)	Cardiac catheterization	71	87	1.47	0.3 mg/dL increase in SCr within 48 h	NR	NR
Katagiri et al, ⁵³ 2012	Japan	77	28 (36.4%)	CPB surgery	64	61	0.97	AKIN criteria within 72 h	NR	-80°C
Nickolas et al, ⁵⁴ 2012	German y	12 12	94 (7.7%)	Emergency ward	NR	47	NR	NA	Yes	-80°C
Matsui et al, ⁵⁵ 2012	Japan	85	48 (56.5%)	CPB surgery	72	75	NR	AKIN criteria within 48 h	NR	-80°C
Li et al, ⁵⁷ 2012	China	25	11 (44%)	Liver transplantation	47	88	0.59	AKIN criteria within 48 h	NR	-80°C

Note: All studies were designed as prospective cohort studies except for Nakamura 2009 and Ferguson 2010, which were cross-sectional studies.

CKD denotes chronic kidney disease; CPB, cardiopulmonary bypass; NR denotes not reported; RIFLE, Risk, Injury, Failure, Loss, End-Stage; AKIN, Acute Kidney Injury Network. SCr, serum creatinine; NA, not applicable; eGFR, estimated glomerular filtration rate

^{*} Scientific abstract;

[†] mean serum creatinine in patients who developed AKI was 2.8 mg/dl

^{**} mean values

^{***} values given as number (percentage).

Table 2
Performance characteristics of urinary L-FABP in the studies included in the systematic review

Study	No. of patients				L-FABP cut-off (ng/mg) ^{**}	Sensitivity (95% CI)	Specificity (95% CI)	AUC-ROC (95% CI)	Timing of measurement
	True-positive	False-positive	False-negative	True-negative					
Development of AKI									
Portilla et al. ³⁸ 2008	15	6	6	13	486	71.4 (61.5-81.3)	68.4 (57.8, 79.1)	0.810 (NR)	4 h post cardiac surgery
Ferguson et al. ⁴⁴ 2010	87	11	5	57	26	95.0 (88.0, 98.0)	84.0 (73.0, 92.0)	0.960 (0.920, 0.980)	Day of nephrology consultation
Nozue et al. ⁵⁶ 2010	2	5	2	86	>33.9 ^{**}	50.0 (NR)	95.0 (NR)	0.610 (NR)	1 d after cardiac catheterization
Matsui et al. ⁴⁷ 2011	12	0	2	11	44	86.0 (NR)	100 (NR)	0.950 (NR)	ICU admission
Doi et al. ³³ 2011 [#]	41	50	25	158	76	62.1 (56.2, 68.1)	76.0 (73.0, 78.9)	0.698 (0.621, 0.765)	ICU admission
Krawczeski et al. ⁴⁸ 2011	NR	NR	NR	NR	NR	NR	NR	0.780 (NR)	12 h post cardiac surgery
Cho et al. ⁴⁹ 2011 [*]	NR	NR	NR	NR	NR	NR	NR	0.796 (0.700, 0.892)	ICU admission
Shang et al. ⁵⁰ 2011 [*]	NR	NR	NR	NR	NR	NR	NR	0.844 (NR)	Immediate period post cardiac surgery
Manabe et al. ⁵² 2012	NR	NR	NR	NR	25	82.0 (NR)	69.0 (NR)	0.700 (NR)	Prior to cardiac catheterization
Matsui et al. ⁵⁵ 2012									
	37	3	11	34	55	77.0 (71.0, 83.0)	92.0 (87.0, 96.0)	0.860 (0.780, 0.940)	Immediate period post cardiac surgery
	35	6	12	29	68	74.0 (68.0, 81.0)	83.0 (76.0, 89.0)	0.85 (0.770, 0.930)	3 h post cardiac surgery
Katagiri et al. ⁵³ 2012	27	31	1	18	89	92.9 (NR)	44.9 (NR)	0.720 (0.590, 0.820)	4 h post cardiac surgery
Nickolas et al. ⁵⁴ 2012	NR	NR	NR	NR	NR	NR	NR	0.710 (0.650, 0.760)	Hospital admission
Li et al. ⁵⁷ 2012	8	4	3	10	3,452	72.7 (NR)	71.4 (NR)	0.760 (0.554, 0.965)	4 h post surgery
Dialysis requirement									
Hamasaki et al. ⁴⁰ 2008 [#]	4	13	0	0	24,897	90.0 (NR)	3.6 (NR)	NR	Day of nephrology consultation (established AKI during hospitalization)

Study	No. of patients				L-FABP cut-off (ng/mg)**	Sensitivity (95% CI)	Specificity (95% CI)	AUC-ROC (95% CI)	Timing of measurement
	True-positive	False-positive	False-negative	True-negative					
Arthur et al, ⁴⁶ 2010 *	NR	NR	NR	NR	NR	NR	NR	0.800 (NR)	At least AKIN stage 1 after CPB
Doi et al, ³³ 2011 #	14	43	13	269	393	63.0 (53.7, 72.3)	78.2 (75.9, 80.5)	NR	ICU admission
Katagiri et al, ⁵³ 2012	3	39	0	35	414	100 (NR)	47.3 (NR)	NR	4 h post cardiac surgery
Non-recovery of kidney function									
Shang et al, ⁵⁰ 2011 *	NR	NR	NR	NR	NR	NR	NR	0.775 (NR)	Immediate period post cardiac surgery
In-hospital mortality									
Doi et al, ²⁵ 2010 #	68	1	0	76	1,800	99.3 (89.5, 100)	98.7 (97.4, 99.9)	0.993 (0.956, 0.999)	ICU admission
Doi et al, ³³ 2011 #	12	97	2	228	113	92.9 (86.0, 99.7)	79.1 (76.8, 81.3)	0.896 (0.835, 0.937)	ICU admission
Cho et al, ⁴⁹ 2011 *	NR	NR	NR	NR	45	72.0 (NR)	70.0 (NR)	0.743 (0.635, 0.851)	ICU admission
Shang et al, ⁵⁰ 2011 *	NR	NR	NR	NR	NR	NR	NR	0.893 (NR)	Immediate period post cardiac surgery
Katagiri et al, ⁵³ 2012	2	52	0	23	810	83.3 (NR)	30.9 (NR)	NR	4 h post cardiac surgery

L-FABP, liver-type fatty acid-binding protein NR-not reported; CI, confidence interval; AUROC, area under the receiver operating characteristic curve; ICU, intensive care unit; CPB, cardiopulmonary bypass; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network

* Scientific abstract

** Urinary level.

Data received directly from corresponding author,

** change level from baseline; ng/ml

Table 3

Summary accuracy of urinary L-FABP for outcome prediction

Outcome prediction	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)**	P-value	Assessment of heterogeneity**	
							I ² index	Q test P value
Acute kidney injury	7	687	74.5% (60.4, 84.8)*	77.6% (61.5, 88.2)*	2.69 (1.63, 4.43)	<0.001	41%	0.1
Dialysis requirement	3	436	69.1% (34.6, 90.5)**	42.7% (3.1, 94.5)**	2.24 (0.53, 9.50)	0.3	36%	0.2
In-hospital death	3	561	93.2% (66.2, 99.0)**	78.8% (27.0, 97.4)**	13.72 (1.96, 95.89)	0.008	51%	0.1

Note: Sensitivity and specificity are given as estimated percentages..

L-FABP, liver-type fatty acid-binding protein; CI, confidence interval; DOR, diagnostic odds ratio

* Derived from bivariate-model meta-analysis

** Derived from random-effects model meta-analyses;