RANDOX

HEART - TYPE FATTY ACID - BINDING PROTEIN (H - FABP)

A CLINICAL DIAGNOSTIC MARKER FOR CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY

A Clinical Diagnostic Marker for Cardiac Surgery-Associated Acute Kidney Injury

1. BACKGROUND

Acute kidney injury (AKI) is defined as a sudden decline in renal function, ranging from minor to complete loss, taking only a few hours to a few days to happen. AKI can have many different causes, but is usually a secondary complication due to decreased blood flow to the kidneys, direct damage to the kidneys or a blockage of the urinary tract. Consequently, unpleasant side effects include: impaired clearance and regulation of homeostasis, altered acid / base and electrolyte regulation and impaired volume regulation [1].

The mortality rate associated with AKI varies depending on severity, patient related factors and setting including whether the patient is in the intensive care unit (ICU) [2]. It is believed that 8 - 16% of admissions to the emergency department (ED) are due to AKI [3]. In the UK, AKI affects a fifth of patients admitted to the ED and has been found to be deadlier than a heart attack, contributing to around 100,000 deaths each year [4]. Conversely, in the US, age - standardised rates of AKI hospitalisations increased by 139% among adults with diagnosed diabetes and by 230% among those without diabetes [5]. Moreover, the majority of AKI cases ollur in low and lower middle income countries, accounting for 1.4 million deaths [3].

The rising incidence of AKI comes at a price. AKI patients will often be discharged from the ICU with various degrees of chronic kidney disease (CKD), placing an increasing strain on health care systems. At present, the cost to the UK's National Health Service (NHS) is estimated to be between £434 and £620 million, which is more than the costs associated with breast cancer, or lung and skin cancer combined [2,3]. However, this increased cost and strain could be avoided, indeed research has shown that 30% of the reported 100,000 deaths in the UK could have been prevented with the right care and treatment [4,5].

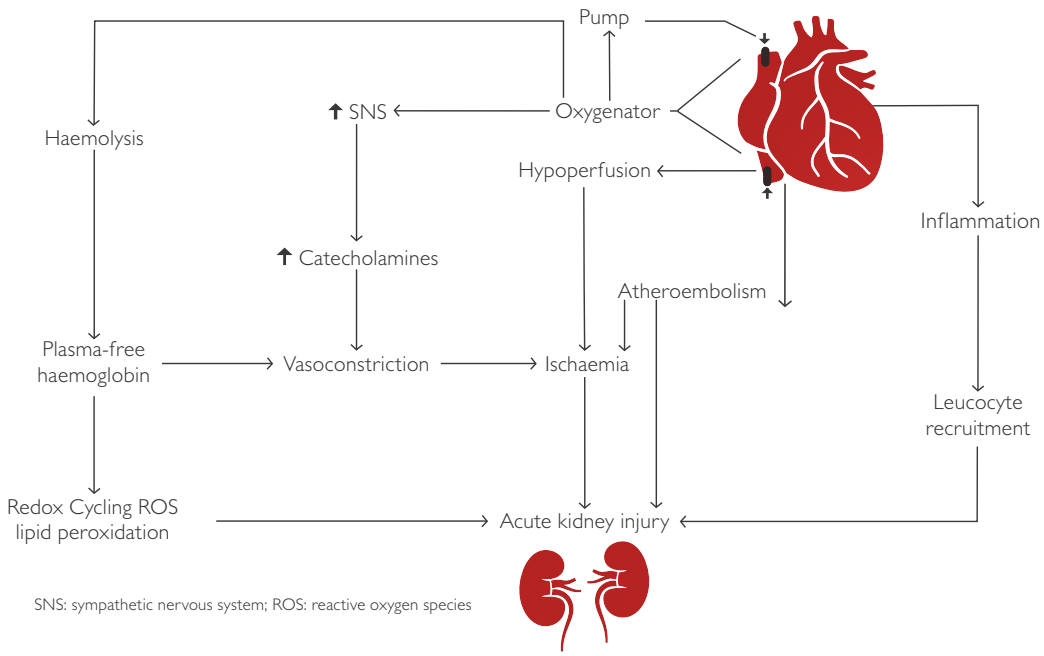
These unfavourable statistics are due, in part, to the late detection of AKI. Serum creatinine (SCr) is still used routinely despite the knowledge that up to 50% of renal function can be lost before significant SCr levels become detectable [5].

2. CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY (CSA-AKI)

CSA-AKI is a well-recognised postoperative complication of cardiac surgery and is the second most common cause of AKI in the ICU, occurring in up to 30% of patients [6,7]. Of these patients, an estimated 1% will require dialysis and the majority will remain dialysis dependent. Certain patient groups are more susceptible to CSA-AKI and vulnerability can depend on age, sex, pre-existing cardiac dysfunction, pre-existing CKD, previous cardiac surgery or comorbidity [8].

The pathogenesis of AKI involves multiple pathways including haemodynamic, inflammatory and nephrotoxic factors that overlap eventually leading to kidney injury [6]. Fig 1 illustrates the pathophysiology of AKI following cardiac surgery, illustrating the multiple physiological processes that are associated with the development of AKI following cardiac surgery [9].

Fig 1: Pathophysiology of AKI following cardiac surgery and the various mechanisms that contribute [9]



SNS: sympathetic nervous system; ROS: reactive oxygen species

3. INTRODUCTION TO H-FABP

Fatty acid-binding proteins (FABPs) are small cytoplasmic proteins that are abundantly expressed in tissues with an active fatty acid metabolism, with their primary function being the facilitation of intracellular long-chain fatty acid transport [10]. Elevated FABP serum concentrations are related to a number of common comorbidities including: myocardial infarction (MI), heart failure, CKD, diabetes mellitus and metabolic syndrome, all of which represent important risk factors for post-operative AKI [11].

Heart-type fatty acid-binding protein (H-FABP) is most commonly used as a marker for MI as it is released 30 minutes following an ischaemic episode and concentrations peak at approximately 6-8 hours following chest pain onset [12]. However, recently H-FABP has been demonstrated to offer utility in the detection of AKI following cardiac surgery. Measurement of H-FABP pre and post cardiac surgery could identify those at a high-risk of AKI and assist in the development of an effective treatment plan, reducing mortality rates and the costs to health services.

4. DIAGNOSTIC VALUE OF H-FABP IN CSA-AKI

1. Scientific Reports (2019): Stratifying risk of acute kidney injury in pre and post cardiac surgery patients using a novel biomarker-based algorithm and clinical risk score [13]

Objective: A Northern Irish study prospectively evaluated 401 cardiac patients who were consecutively scheduled for elective cardiac surgery within the Cardiac Surgical Unit of the Royal Victoria Hospital, Belfast, Northern Ireland between May 2012 and August 2013. Upon the exclusion of those <18 years of age, pre-operative or pre-trauma dialysis-dependent renal failure, or known significant diseases, active malignancies, active endocarditis, sepsis, septic/cardiogenic shock, or had pre-operative haemodynamic instability prior to entrance into the study, 344 of the 401 cardiac patients were recruited.

Findings:

Table 1: Serum biomarkers for predicting AKI pre and post cardiac surgery [13]

Anytime	Biomarkers	AUROC	CI		
Pre-operative	$sTNFR_2$	0.713	0.647 - 0.778	65.6% (42/64)	0.32 (0.18-0.56)
	$sTNFR_1$	0.748	0.684 - 0.812	70.3% (45/64)	68.5% (188/260)
Post-operative	MK	0.704	0.633 - 0.775	70.7% (41/58)	61.3% (130/212)
	H-FABP	0.729	0.633 - 0.794	63.1% (41/65)	61.8% (177/257)
	$sTNFR_2$	0.726	0.699 - 0.825	69.2% (45/65)	69.2 (175/253)
	$sTNFR_1$	0.774	0.708 - 0.840	72.3% (47/65)	74.0% (188/254)
	H-FABP+MK+$sTNFR_1$	0.836	0.761 - 0.872	81.0% (47/58)	67.8% (141/208)
	H-FABP+MK+$sTNFR_2$	0.836	0.785 - 0.888	75.9% (44/58)	69.1% (143/207)

AKI: acute kidney injury; AUROC: area under the reciever operating characteristics; CI: confidence interval; sTNFR1: soluble tumour necrosis factor receptor -1; sTNFR2: soluble tumor necrosis factor receptor -2; MK: midkine; H-FABP: heart-type fatty acid binding-protein.

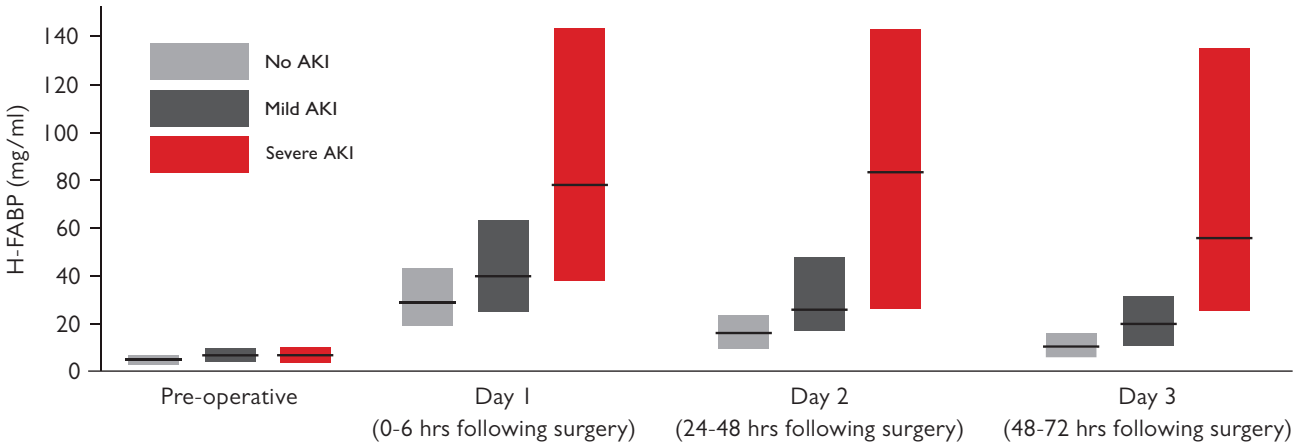
Conclusion: Post-operatively, a combination of H-FABP, MK and sTNFR1 or sTNFR2 offered the highest predictive ability to identify patients at risk of developing AKI.

2. Kidney International (2015): Peri-operative heart - type fatty acid - binding protein is associated with acute kidney injury after cardiac surgery [14]

Objective: Data was utilised from the Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) cohort study; a multi-centered cohort of 1,219 patients who underwent cardiac surgery and were at a high risk of developing AKI; to evaluate the association between H-FABP levels and AKI.

Findings: Elevated pre- and post-operative H-FABP levels were observed in patients who experienced any AKI, compared to those who did not experience AKI. The highest pre- and post-operative H-FABP levels were observed in those with severe AKI (fig 2).

Fig 2: Peri-operative H-FABP levels by AKI status [14]



Each bar represents the interquartile (25th to 75th percentile). Horizontal black line represents the median.

Conclusion: Researchers found that the first post-operative (Day 1), H-FABP levels in patients with severe AKI increased by 13-fold and an increase of 8-fold was observed for the same time point in patients who experienced any AKI. In day 2 and 3, H-FABP levels began to decline, however, a slower rate of decline was observed in patients who experienced AKI [13].

Moreover, H-FABP levels have been found to rise in post-operative patients who experienced post-operative MI. It is possible that patients are experiencing pre-renal AKI due to MI following surgery. As a marker of inflammatory injury, elevated post-operative H-FABP levels were observed in patients following on-pump cardiac surgery. Potentially, patients who experienced severe myocardial inflammatory injury also experienced renal inflammatory injury. Elevated levels of post-operative H-FABP could be a biomarker of haemodynamic changes related to delayed recovery of the cardiac tissue following surgery.

During the follow-up period 10.8% of the patient cohort died, these patients presented with high pre-operative H-FABP levels. Patients with elevated pre-operative H-FABP levels were significantly more likely to die compared to patients with normal or low levels. The authors concluded that H-FABP explained <10% of the variability in known AKI biomarkers and it is possible that H-FABP is capturing a different aspect of the pathophysiology of AKI than traditional kidney biomarkers [13].

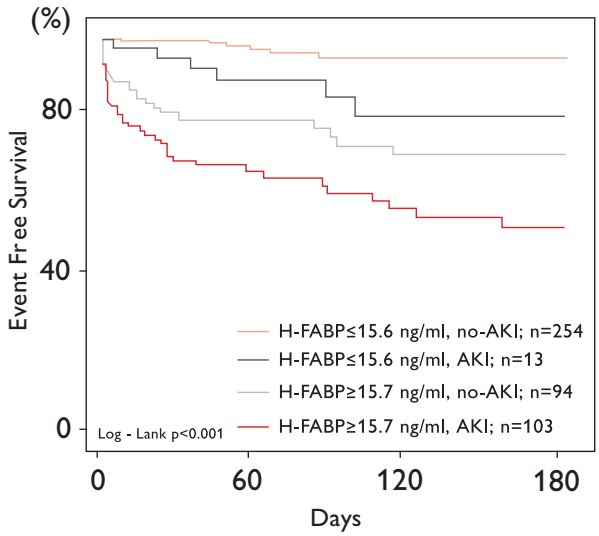
5. PROGNOSTIC VALUE OF H-FABP IN CSA-AKI

1. BMC Cardiovascular Disorders (2016): The serum heart-type fatty acid-binding protein (H-FABP) levels can be used to detect the presence of acute kidney injury on admission in patients admitted to the non-surgical intensive care unit [15]

Objective: Utilising the RIFLE classification, 1,183 patients' cardiac biomarkers, including H-FABP, were screened in the emergency department and 494 non-surgical ICU patients were enrolled on this study to evaluate not only the diagnostic value of H-FABP but also the mid-term prognosis and all cause death within 30-days were also evaluated.

Findings: The Kaplan-Meier survival curve (Fig 3) illustrates that the prognosis, including all-cause mortality, was significantly reduced in the patient group with H-FABP levels ≥15.7 ng/ml with AKI compared to the other three patient groups.

Fig 3: A Kaplan-Meier survival curve comparing the event free survival rate for patients with varying H-FABP levels and AKI diagnosis [15]



	Follow Up Periods			
	60	120	180	
H-FABP≤15.6 ng/ml, no-AKI; n=254	145	104	94	Cases
H-FABP≤15.6 ng/ml, AKI; n=13	29	17	14	Cases
H-FABP≥15.7 ng/ml, no-AKI; n=94	50	37	27	Cases
H-FABP≥15.7 ng/ml, AKI; n=103	46	28	16	Cases

Conclusion: Patients with a H-FABP level of ≤ 15.6 ng/ml with no AKI had nearly a 100% chance of event free survival over the 180 days. In comparison, patients with levels ≥ 15.7 ng/ml, with AKI had a steady decrease in event free survival over the 180 days levelling out at just above 40% [14].

6. METHODOLOGY

Previously, the only method available for H-FABP testing was the ELISA methodology. Today, automated methods are available, offering numerous benefits for the laboratory.

EFFICIENCIES

In a laboratory, employing the ELISA method for clinical testing is notably time and personnel consuming, with heavy resources utilised on manual interaction. Moving from this method to an automated method is considerably more time efficient. The significance of ensuring quality in testing practices and confidence in patient results is a key consideration for running automated biochemistry tests over manual ELISA techniques. The risk of errors and contamination of samples, thereby compromising patient results is greatly reduced using automated methods as opposed to manual methods.

EXPANSION

Automated biochemistry methods enable laboratories to expand their test menu with ease, allowing the inclusion of H-FABP into routine testing panels due to reduced manual work. Automated biochemistry assays increase testing ranges, enabling detailed patient testing profiles without the manual restrictions placed by running ELISA techniques.

Randox is currently one of the only diagnostic manufacturers who offer an automated biochemistry test for H-FABP measurement worldwide.

7. RANDOX AUTOMATED H-FABP ASSAY

The Randox H-FABP assay utilises the latex enhanced immunoturbidimetric method offering superior performance and producing results within 14 minutes. The Randox H-FABP assay offers the following key benefits:

- **A niche product from Randox** meaning that Randox are one of the only manufacturers to offer the H-FABP test in an automated clinical chemistry format.
- **An exceptional correlation** coefficient of r=0.97 when compared against commercially available methods.
- **CE marked for diagnostic use.**
- **Wide measuring range** of 0.747 - 120ng/ml for the early detection of clinically important results.
- **Liquid ready-to-use format** for convenience and ease-of-use.
- **Dedicated H-FABP calibrator and controls available** offering a complete testing package.
- **Applications available** detailing instrument-specific settings for the convenient use of the Randox H-FABP assay on a variety of clinical chemistry analysers.

The Randox automated L.E.I H-FABP assay offers an improved method for the assessment of CSA-AKI combined with a convenient format for routine clinical use, enabling physicians to accurately evaluate at risk patients.

8. CONCLUSION

CSA-AKI is a well-recognised postoperative complication of cardiac surgery and is the second most common cause of AKI in the ICU, occurring in up to 30% of patients [6, 7]. Of these patients, an estimated 1% will require dialysis and the majority will remain dialysis dependent. Certain patient groups are more susceptible to CSA-AKI and vulnerability can depend on age, sex, pre-existing cardiac dysfunction, pre-existing CKD, previous cardiac surgery or comorbidity 8. The pathogenesis of AKI involves multiple pathways including haemodynamic, inflammatory and nephrotoxic factors that overlap eventually leading to kidney injury [6].

H-FABP has been identified as a marker of CSA-AKI in several studies, both in diagnosis and prognosis. Post-operatively, a combination of H-FABP, MK and sTNFR1 or sTNFR2 offered the highest predictive ability to identify patients at risk of developing AKI [13].

The Randox automated L.E.I H-FABP assay offers an improved method, combined with a convenient format for routine clinical use, for the assessment of at risk patients. Randox is currently one of the only diagnostic manufacturers who offer an automated biochemistry test for H-FABP measurement worldwide.

9. REFERENCES

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