The effect of acute changes in glomerular filtration rate on common biochemical tests

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A B S T R A C T

Objectives: To characterise the effect of acute kidney injury on the concentration of common biochemical analytes.
Design: and methods: Pairs of serum or plasma samples from the same patients routinely submitted to the laboratory were subject to further analysis based on changes in serum creatinine within 72 h. Samples collected from patients on dialysis were excluded. Samples were measured for 28 biochemical analytes including electrolytes, liver function tests, iron studies, creatine kinase, amylase, lipase, parathyroid hormone, troponin T and troponin I, B-natriuretic peptide and NT pro B-natriuretic peptide.
Results: 148 sample pairs were included with 99 having a rise in serum creatinine >50%, 18 with a fall of >50% and 31 with smaller changes. Acute changes in renal function were associated with changes in the concentration of several analytes, with the changes of the greatest magnitude observed in urea, phosphate, urate, parathyroid hormone, troponin T, BNP and NT-ProBNP. The remaining analytes did not show significant changes with changes in renal function.
Conclusion: Acute changes in renal function are associated with significant changes in concentration of some serum/plasma biochemical analytes but not others. Expected changes in analyte concentration must be considered in the setting of acute kidney injury to avoid misinterpretation of blood test results.

1. Introduction

Acute kidney injury (AKI) is a common disorder in hospital inpatients defined by rapid changes in glomerular filtration rate (GFR) [1,2]. Blood pathology testing may be requested in patients with worsening AKI as well as in the recovery phase. Changes in renal function are expected to alter the circulating concentration of biochemical analytes that undergo renal handling. The strong effect of renal function on creatinine and urea levels is recognised as these biomarkers are used to monitor the progress of renal impairment and recovery. Many other biochemical analytes similarly undergo renal excretion or metabolism and may likewise be expected to vary in concentration with glomerular filtration rate and some, for example cystatin C, are used for this purpose [3]. In contrast to tests that

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may be used for diagnosis or monitoring of GFR changes, other tests are required when patients have other conditions together with AKI. In these settings an understanding of the effects of changes in GFR is required to assist with interpretation of such tests. In general there is limited literature on the effects of acute changes in GFR on common biochemistry tests and so we sought to characterise the effect of AKI on the concentration of a range of analytes commonly measured in the biochemistry laboratory.

2. Materials and methods

The study used samples submitted to the laboratory for routine clinical purposes. Pairs of samples were identified when an inpatient demonstrated a >50% change (increase or decrease) in creatinine concentration within a 72 h interval. Additional sample pairs with changes in creatinine of less than 50% in this time frame were also included to provide a continuous data set. Lithium heparin samples were collected on all subjects and EDTA samples were included if they had also been collected. Subjects were excluded if patients were known to be undergoing dialysis or if patient age was less than 18 years. Samples were de-identified and stored at −20 °C prior to analysis up to a maximum of 9 days, with each pair of samples from a patient analysed in the same analytical run. 26 biochemical analytes including electrolytes, liver function tests, iron studies, creatine kinase, amylase, lipase, urate, troponin T, NT-proBNP and parathyroid hormone (PTH) were measured on all heparin samples using a Roche Modular analyser (see Table 1 for included analytes, analyser and sample numbers). Troponin I and B-natriuretic peptide (BNP) were measured on an Abbott Architect using EDTA samples. All analytes were stable under these storage conditions. Demographic data collected was patient sex and age decade.

Data analysis was performed in Microsoft Excel. For each sample pair, the percentage change in creatinine concentration (∆Creatinine) was calculated. This served as a proxy for changes in GFR. For example, a halving of GFR would be anticipated to result in an approximate doubling of creatinine concentration, or a ∆Creatinine of +100%. A stable GFR as indicated by an unchanged creatinine concentration corresponds to a ∆Creatinine of 0%.

For each sample pair, the percent change in analyte concentration (∆Analyte) was calculated in a similar manner. A plot of ∆Analyte against ∆Creatinine enabled visualization of the change in analyte concentration as a function of change in creatinine.

To facilitate analysis, results were stratified into five groups according to ∆Creatinine. For each group, median ∆Analyte values were determined. The overall relationship between the analyte of interest and creatinine was characterised by the slope obtained by linear regression of the median ∆Analyte values for each subgroup. Statistical significance (p-value < 0.05) of the linear regression being different from a slope of zero was determined for each analyte. As an indication of possible clinical significance, the median change of each analyte in each group was compared with the Reference Change Values for each analytes based on the within-subject biological variation and the measurement repeatability (see Table 1). Biological variation data was taken from the ELFM database (biologicalvariation.eu) where available and other sources if not included at that site.

Ethics approval for this study was granted by St Vincent's Hospital Sydney Human Research Ethics Committee.

Table 1

Sample pair numbers (n),Within-subject biological variation (CV_I), repeatability precision (CV_R) and Reference Change Values (RCV) for the included analytes as well as median, 10th and 90th centiles on analyte concentrations for the 1st samples in the pairs.

Test Name	n	CV_I	CV_R	RCV	Median	10th centile	90th Centile	Units
Albumin	148	2.5%	0.7%	6.9%	34	27	40	g/L
ALP	148	5.3%	0.7%	14.7%	73	40	163	U/L
ALT	148	10.1%	2.2%	28.0%	23	10	62	U/L
Amylase	148	6.6%	0.3%	18.3%	47	25	147	U/L
AST	148	9.6%	1.4%	26.6%	30	16	108	U/L
Bicarbonate	147	4.0%	1.4%	11.1%	22	17	27	mmol/L
Bilirubin	148	20.0%	1.4%	55.4%	7.0	2.6	31.7	umol/L
Calcium	148	1.8%	0.5%	5.0%	2.19	1.87	2.52	mmol/L
Chloride	148	1.1%	0.6%	3.0%	98	90	103	mmol/L
Creatine Kinase	148	15.0%	0.4%	41.6%	92	20	1311	U/L
Creatinine	148	4.5%	1.1%	12.5%	92	50	249	umol/L
Ferritin	148	12.8%	1.7%	35.5%	401	113	1370	ug/L
GGT	148	9.1%	1.0%	25.2%	52	13	239	U/L
Iron	148	20.7%	0.7%	57.3%	7.2	2.7	22.6	umol/L
LDH	147	5.2%	0.4%	14.4%	587	393	1075	U/L
Lipase	148	9.2%	0.9%	25.5%	27	10	107	U/L
Magnesium	148	2.9%	0.4%	8.0%	0.87	0.63	1.35	mmol/L
Phosphate	148	7.8%	0.4%	21.6%	1.17	0.72	1.80	mmol/L
Potassium	148	4.1%	0.9%	11.4%	4.8	3.8	5.8	mmol/L
Protein	148	2.6%	0.4%	7.2%	60.0	47.2	7.4	g/L
Sodium	148	0.5%	0.3%	1.4%	137	130	143	mmol/L
Transferrin	148	3.9%	1.3%	10.8%	1.64	1.02	2.65	g/L
Urate	148	8.3%	0.5%	23.0%	0.292	0.114	0.603	mmol/L
Urea	148	13.9%	1.0%	38.5%	7.7	3.5	20.3	mmol/L
PTH	147	15.7%	1.3%	43.5%	4.9	2.1	17.7	pmol/L
Troponin T	148	14.0%	3.0%	38.8%	44.7	10.2	610.2	ng/L
NT-proBNP	148	10.0%	1.7%	27.7%	1550	144	15163	ng/L
BNP	99	29%	3.8%	80.3%	151	26	882	ng/L
Troponin I	127	14%	4.2%	38.8%	36.5	4.5	1642	ng/L

3. Results

148 sample pairs were included for analysis on most analytes (see Table 1). The population had a median age in the 60s (range 20s–90s) and 58% were male. Ninety nine subjects showed an increase in plasma creatinine greater than 50%, 18 showed a fall in plasma creatinine >50% and 31 sample pairs has lesser changes. The demographic characteristics and first creatinine concentrations of the analysis groups are shown in Table 2. The median time between samples was 48 h (range 6–72 h).

The changes in analyte concentration relative to the change in creatinine concentration are presented in Table 2. Acute changes in renal function, as indicated by a change in creatinine concentration, were associated with a statistically significant ($p < 0.05$) change in concentration of several analytes: urea, ALP, bicarbonate, urate, magnesium, phosphate, ferritin, troponin T and PTH. All of these analytes increased with increasing creatinine with the exception of bicarbonate. As a guide to the indication of likely clinical significance, the median changes in at last one data group exceeded the reference change values for all these analytes with the exception of ferritin (Table 1).

While for most analytes the pattern of change was consistent across increasing and decreasing ΔCreatinine, for NT-proBNP and BNP a "U-shaped" pattern was seen. The analysis was performed excluding the subgroup with falling creatinine. With this exclusion, NT-proBNP showed statistical and likely clinical significance, however the relationship between BNP concentrations and creatinine did not reach statistical significance despite median concentration changes being found to increase in parallel with creatinine.

The slope of the median percentage change in analyte concentration vs. percentage change in creatinine indicates that the strength of the relationship was greatest for NT-proBNP (slope 1.10), followed by urea (slope 0.83), urate (0.54), troponin T (0.53), phosphate (0.48), and PTH (0.34). The strength of the relationship for bicarbonate, calcium, magnesium and ferritin was low despite attaining statistical significance. For instance, a 50% increase in creatinine was related to a median 2% decrease in bicarbonate concentration.

Table 2
Change in analyte concentration relative to change in creatinine and demographic data. Results are separated based on ΔCreatinine. Analytes are listed according to change relative to creatinine change. Changes in bold indicate a median change greater than the Reference Change Value for that analyte.

Analytes	Analyte median percent change					Change Relative to Δcreatinine	
	Stratified by percent change in creatinine						
	< -40%	−40% to 40%	40% to 75%	75% to 100%	>100%	Slope (95% CI)	p-value
BNP	60%	8%	17%	54%	**167%**	1.12 (−0.84, 3.09)[a]	0.133
NT-ProBNP	23%	−2%	**31%**	**58%**	**141%**	1.10 (0.02, 2.19)[a]	0.049
Urea	**−56%**	10%	**49%**	**71%**	**102%**	0.83 (0.69, 0.97)	0.0003
Urate	**−57%**	1%	**26%**	**33%**	**47%**	0.54 (0.28, 0.80)	0.007
TnT	−37%	−5%	24%	**42%**	**61%**	0.53 (0.49, 0.57)	0.00002
Phosphate	**−52%**	0%	**27%**	**23%**	**40%**	0.48 (0.20, 0.75)	0.012
PTH	−15%	7%	24%	**44%**	**44%**	0.34 (0.20, 0.47)	0.004
Ferritin	−13%	−1%	5%	4%	21%	0.16 (0.06, 0.26)	0.016
Magnesium	−3%	−1%	**11%**	**15%**	**26%**	0.15 (0.07, 0.23)	0.009
Bilirubin	−10%	6%	7%	7%	10%	0.10 (0.00, 0.20)	0.055
Creatine Kinase	−37%	−21%	−20%	−18%	−20%	0.09 (−0.02, 0.20)	0.090
Amylase	**−20%**	1%	0%	−10%	−2%	0.07 (−0.12, 0.25)	0.341
ALT	−18%	−2%	−3%	−9%	−4%	0.05 (−0.08, 0.18)	0.290
ALP	−4%	6%	4%	5%	1%	0.03 (−0.07, 0.12)	0.440
Potassium	6%	−8%	0%	−1%	7%	0.02 (−0.13, 0.16)	0.766
Albumin	−5%	0%	1%	−1%	0%	0.02 (−0.02, 0.07)	0.191
LDH	−9%	−3%	−8%	1%	−5%	0.02 (−0.06, 0.11)	0.452
TnI	19%	−11%	0%	−4%	24%	0.02 (−0.35, 0.39)	0.873
Total protein	0%	1%	0%	2%	1%	0.00 (−0.02, 0.02)	0.742
AST	−3%	−7%	−4%	−5%	−6%	−0.01 (−0.04, 0.02)	0.404
Sodium	**2%**	−1%	−1%	**−2%**	−1%	−0.02 (−0.04, 0.00)	0.052
Calcium	2%	0%	0%	−1%	−5%	−0.03 (−0.06, 0.00)	0.034
Chloride	**8%**	−1%	−1%	−3%	−3%	−0.05 (−0.11, 0.00)	0.058
Bicarbonate	6%	−2%	−2%	−4%	−4%	−0.05 (−0.09, −0.01)	0.033
GGT	3%	5%	−4%	4%	−8%	−0.05 (−0.16, 0.06)	0.243
Transferrin	−4%	−1%	−3%	−6%	**−13%**	−0.05 (−0.13, 0.04)	0.176
Lipase	12%	2%	1%	−11%	−2%	−0.09 (−0.21, 0.04)	0.113
Iron	11%	19%	−14%	−28%	−27%	−0.26 (−0.53, 0.00)	0.052
Demographics							
n samples	**19**	**24**	**53**	**24**	**28**		
Sex (% male)	79%	38%	62%	63%	54%		
Age (decades, median, range)	60 (50,90)	60 (30,90)	50 (20,90)	60 (30,90)	50(20,90)		
1st Creatinine (umol/L)	228 (165,333)	74 (59,106)	93 (70,117)	83 (67, 110)	74 (57, 105)		

[a] linear regression performed following exclusion of the lowest ΔCreatinine bin.

4. Discussion

The present study is the first to characterise the effect of changes in creatinine consistent with AKI on the concentration of multiple analytes and to quantitatively determine the relationship between the analyte of interest relative to the change in creatinine concentration. There are very few published studies which have examined the effect of AKI onset and resolution on the concentration of specific biochemical analytes in case series.

The effect of onset and resolution of AKI on some analytes is unsurprising given the significant role of renal handling in elimination. These include urea, urate, phosphate, PTH, troponin T, BNP and NT-proBNP (Fig. 1a–g). The magnitude of the slope between the change in analyte concentration and creatinine concentration were the greatest for these analytes. Changes in concentration of these analytes have previously been described in limited case series. Changes in urea concentrations demonstrated one of the strongest links to changes in renal function with the percentage change in urea level approximating 0.83 of that of creatinine (Fig. 1a). This finding is consistent with the well-known observation of elevated urea in AKI [4].

Urate concentrations were also significantly related to creatinine concentrations with percentage increases in urate approximating 0.54 of the relative increase in creatinine. Urate concentrations have been related to kidney disease, however the exact nature of the relationship remains unclear, with urate thought to be both a predictor as well as a consequence of AKI [5]. In this study we observed elevations in urate concentration occurring in parallel to changes in creatinine, even within the short time frame used in this study (Fig. 1b). This observation is consistent with the increase in urate concentration being a consequence of AKI.

Changes in phosphate and PTH concentrations were significantly related to changes in renal function (Fig. 1c and d). Phosphate and PTH levels have previously been described in cohort studies of acute kidney injury with elevated phosphate a common finding [4,6]. In one case series, PTH levels were observed to be high, however were not significantly elevated in a second case series [7,8]. This study clearly demonstrates that changes in phosphate and PTH levels are a feature of evolving AKI and should be expected to occur alongside changes in creatinine.

Cardiac biomarkers such as troponins and BNP have been previously described in the context of predictors of AKI outcome,
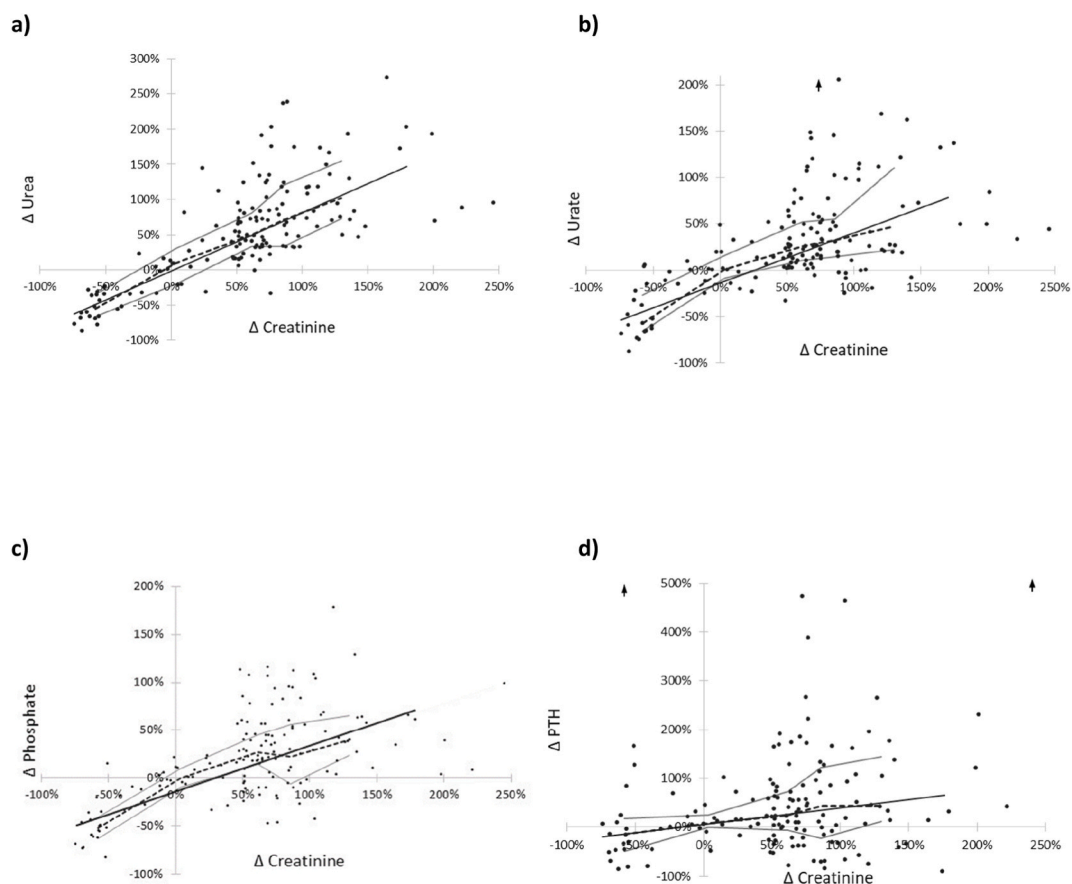

Fig. 1. Change in analyte concentration (ΔAnalyte) relative to ΔCreatinine.**Dots are individual data points, arrows indicate samples outside the selected y-axis range. The dashed line (median) and dotted lines (25th and 75th centiles) relate to the subgroups based on ΔCreatinine; Solid line – linear regression of group medians (excluding lowest group for BNP and NT-proBNPP).** a) Urea, b) Urate, c) Phosphate, d) PTH, e) BNP, f) NT-pro-BNP, g) Troponin T, h) Troponin I.
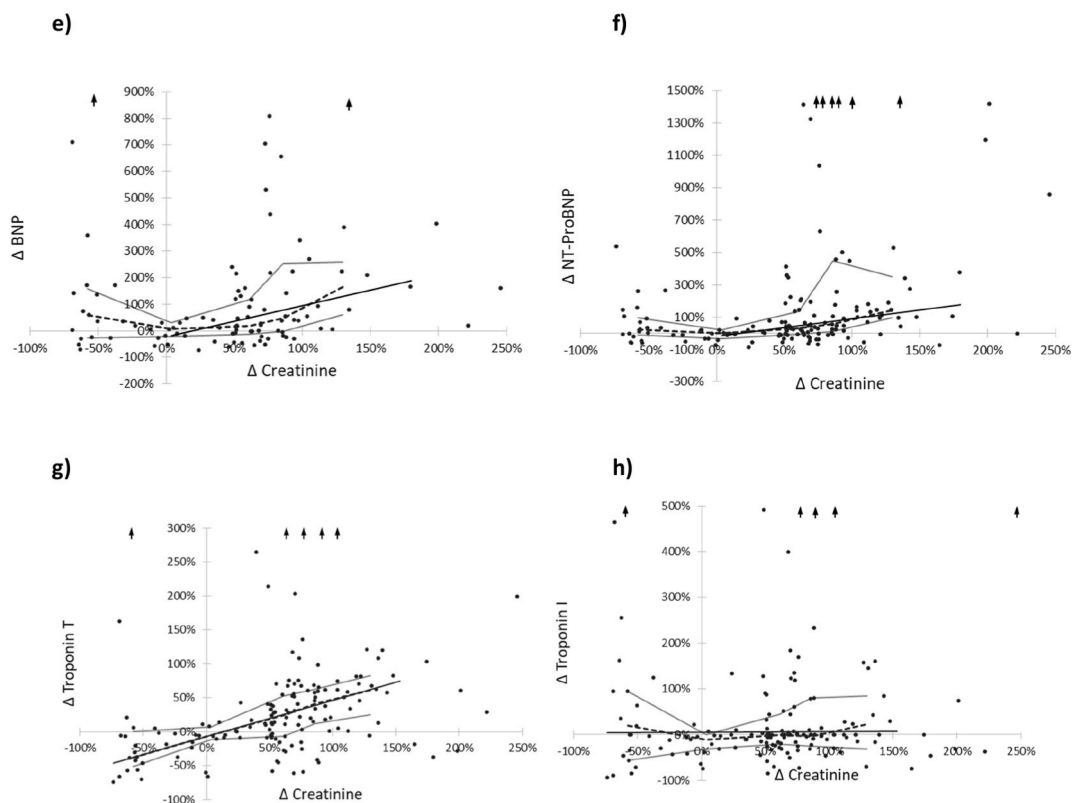
e)

f)

g)

h)

Fig. 1. (*continued*).

however few case series have examined dynamic changes in these markers in evolving AKI. One case series demonstrated statistically significant elevations of BNP in ICU patients with AKI [9]. In another series, NT-ProBNP on admission was observed to be associated with AKI in ICU, however changes in NT-ProBNP concentrations were not described as AKI progressed [10]. The present study observed increases in both BNP and NT-ProBNP in parallel with creatinine as renal function declined (Fig. 1e and f). As AKI resolved, concentrations of BNP and NT-ProBNP did not decline in parallel with creatinine. This may reflect separate pathophysiology, which may be related to AKI, leading to prolonged elevations in BNP and NT-ProBNP. In this study the changes in NT-proBNP met statistical significance, whereas BNP did not. The general trend indicates an increase in natriuretic peptide levels in parallel with changes in creatinine, however a considerable scatter of results is also evident with many paired samples demonstrating a decrease in natriuretic peptide concentration with increasing creatinine. The observed scatter may in part be attributed to the combination of both biological and analytical variability of BNP and NT-proBNP. The underlying pathophysiology of AKI, which was not ascertained, may also have a direct bearing on natriuretic levels.

Troponin T levels were observed to change in relation to acute renal impairment, however in contrast this was not observed for Troponin I (Fig. 1g and h). Troponin concentrations in renal failure have been widely described however only a few case series have examined troponins in the context of evolving acute renal failure. Both troponin T and troponin I concentrations were found to be associated with AKI in a cohort of ICU patients, however the change in these levels as AKI progressed was not described [10]. A case series of 3 patients described increases in troponin T in the context of rhabdomyolysis-induced AKI with no parallel increase in Troponin I [11], however this may be confounded by non-specificity of the troponin T assay utilised. The present study demonstrates contrasting effects of AKI on changes in troponin T concentrations and troponin I concentrations, with the latter being largely unaffected. This study suggests that acute renal impairment should be expected to result in an elevation of Troponin T results, with a 50% increase in creatinine expected to produce an approximate 25% increase in Troponin T levels over baseline. In contrast, Troponin I concentrations are not expected to be influenced by acute changes in renal function. Together, these observations suggest that troponin I as an alternative to troponin T measurement are preferable in the setting of unstable renal function.

Electrolytes such as sodium, chloride, calcium and magnesium did not demonstrate pronounced changes in the setting of acute changes in renal function. Although a decrease in bicarbonate and total calcium levels with increasing creatinine met the threshold for statistical significance, the magnitude of this correlation was low (slope -0.05 and -0.03 respectively). Significant changes in potassium were not observed. Hyperkalaemia and hypocalcaemia have been described in patients with AKI [6,12]. In the present study, increases in potassium were observed in parallel to increases in creatinine for some patients, however other patients demonstrated decreases in potassium with the result of no overall trend. Overall the group medians for none of these analytes exceeded reference change values.

The serum enzymes AST, ALT, GGT, ALP, CK and LDH examined in the present study are large molecules which do not undergo significant renal handling. These were observed to remain unchanged in renal impairment. One case series described the findings of elevated AST and bilirubin in sepsis-related AKI, however these may be related to other specific pathology [6]. Albumin and total protein concentrations may have been expected to increase in AKI secondary to dehydration, but no such effect was observed. This may reflect causes of AKI other than dehydration. Similarly, no clear changes in concentration were observed for ferritin, iron or transferrin. Amylase and lipase are both filtered at the glomerulus, however no increase was observed in AKI in this study. Elevations in amylase concentrations have however been described by others in the context of AKI in patients with no clinical evidence of pancreatitis [13]. Of these analytes, only a fall in serum creatinine >40% was associated with median reductions in amylase more than the RCV.

This study is the first to characterise changes in analyte concentration in relation to changes in renal function. A strength of this study is that analytes were measured on samples regardless of whether or not they were initially requested on clinical grounds. This overcomes the key limitation of selection bias inherent in studies based on data-mining techniques.

A limitation of this study is the considerable scatter observed in the observed relationships. This will include the combination of biological variation and analytical variation in both axes (creatinine and the analyte of interest). Both of these sources of variation also contribute to the reference change value for any particular analyte result to be considered different to the previous result. Although the statistical significance of the study findings were presented, the clinical significance of changes in analyte concentration is dependent on the purpose of testing. Changes in analyte concentration may also reflect underlying pathophysiology depending on the specific cause of AKI, which was not ascertained in this study. The presence of intercurrent disease is also likely to be relevant, for example the troponin results for several patients indicate significant cardiac damage during the sampling period. The criteria of changes relative to the RCV can also be seen as only a rough guide to clinical importance, as the CV_I values have generally been determined in healthy outpatients over longer time periods. The analytical precision can be seen as having a very small contribution to the observed variation as it is small relative to the CV_I in all cases. A further limitation arises from the nature of biomarkers, such as creatinine, being lagging indicators of rapidly changing renal function. However measurements utilised in this study reflect the real-world situation where blood tests by nature provide a point-in-time snapshot amidst a dynamically changing clinical course.

5. Conclusion

In conclusion this novel study provides information on how a number common biochemical analytes vary, or do not vary, with acute changes in renal function. These expected changes in analyte concentration must be considered to accurately interpret blood test results in the setting of acute kidney injury.

Author roles

Graham Jones: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. **Jason Chung:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

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Declaration of competing interest

None.

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