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Acute kidney injury detection with additional point-of-care creatinine vs central laboratory serum creatinine measurement in critically ill patients

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ABSTRACT

Background: Serum creatinine measured by point-of-care testing (CrP) correlates with central laboratory serum creatinine (CrC) measurement and can be performed frequently, which might lead to an earlier diagnosis of acute kidney injury (AKI). We aimed to test whether the combination of CrP and CrC measurement would achieve earlier and more freuent AKI diagnosis than routine CrC testing alone.
Methods: Retrospective study of critically ill patients with two or more CrP measurements 24 h before an AKI was diagnosed on CrC.
Results: 1591 patients with a median APACHE 3 score of 67 (IQR 52-85) and a median number of CrP of 5 (IQR 3-6) measurements. The median individual differences in time to AKI diagnosis between CrC and CrP was −5 h (−11-−1). As the number of point-of-care tests increased in the 24 h before CrC-defined AKI diagnosis, the difference in hours increased (−3 (IQR −6-−1) to −8 (IQR −13– −2); $p < 0.001$). Compared to CrC alone, the use of both CrC and CrP detected more increases in AKI severity to each AKI stage (stage 1: 1767 (34 %) vs 1.170 (30 %); stage 2: 1.301 (25 %) vs 809 (21 %) and stage 3: 2071 (40 %) vs 1920 (49 %); $p < 0.001$).
Conclusion: Combined with CrC, CrP measurement resulted in the earlier diagnosis of AKI during ICU admission. Compared to CrC alone, using CrP measurements in combination with CrC was also associated with a higher maximum AKI stage and more detection of worsening AKI.

1. Introduction

The diagnosis of acute kidney injury (AKI) is based on urine output and serum creatinine [1]. Traditionally, serum creatinine has been seen as a flawed and late biomarker of AKI because it increases only if approximately 50 % of the glomerular filtration rate (GFR) is lost and, therefore, cannot be used to trigger early protective interventions [2]. However, another limitation to the value of creatinine as a biomarker of

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AKI in critically ill patients arises from the fact that it is typically measured in the central laboratory once or, at most, twice a day.

Serum creatinine can now be measured by point-of-care testing (POCT) using arterial blood gas machines. Until recently, little was known about the performance of point-of-care creatinine (CrP), when compared to central laboratory creatinine (CrC) in critically ill patients. Recent research, however, has demonstrated that CrP correlates highly with CrC across the whole range of creatine measurements [3]. Furthermore, though other physiological variables impact the relationship between the two methods, the magnitude of such effects is clinically negligible. Thus, CrP is equivalent to CrC.

A rapid diagnosis of AKI is essential to the management [4] and delayed detection of AKI has been associated with adverse patient outcomes [5,6], more frequent assessment of serum creatinine appears desirable. Given the correlation between central laboratory and POCT creatinine, such assessment could be enabled by CrP. Such frequent creatinine measurements performed multiple times a day and in combination with routine arterial blood gases and continued central laboratory monitoring may allow earlier detection of AKI.

Accordingly, in a large, diverse population of critically ill patients from multiple ICUs, we aimed to test the primary hypothesis that the addition of CrP to CrC measurement would achieve AKI diagnosis significantly earlier than central laboratory creatinine (CrC) measurement only. Moreover, we aimed to test the secondary hypothesis that CrP testing, when combined with routine CrC testing, would detect more patients with stage 2 and stage 3 AKI than routine CrC testing alone.

2. Methods

2.1. Study design

We conducted a multicentre, retrospective cohort study of granular, routinely collected, EMR-based clinical data.

2.2. Study sites and patient identification

The study was conducted at four closed-model tertiary ICUs in Queensland, Australia. The study evaluated all adult patients admitted between January 1, 2015, and December 31, 2021. There were no clinical exclusion criteria. Patients were included in the study if greater than 50 % of their arterial blood gas analyses included a creatinine measurement, they had two or more POCTs performed within 24 h before CrC-determined AKI diagnosis, and their length of stay was greater than 24 h.

2.3. Data sources

Data was collected from all centres using eCritical MetaVision™ (iMDsoft, Boston, MA, USA) clinical information systems [7–10], the ANZICS CORE Adult Patient Database (APD) [11–14], the Queensland Health Admitted Patient Database Collection (QHAPDC) [15–17] and the Queensland Births, Deaths. and Marriage Registry [18,19]. Admission diagnoses were categorised to optimise data accuracy and interpretability (Supplementary Methods, **Table S1**). The Charlson-defined co-morbidities and index were calculated from the ICD-10 codes (Supplementary Methods, **Table S2**) [20,21].

2.4. Creatinine measurement

CrC was measured by Pathology Queensland laboratories on the general chemistry analysers at four hospitals. For all sites during the study period, the central lab measurement was based on the Jaffe rate method [22] and performed on Beckman Coulter general chemistry analysers (Beckman Coulter, Brea, CA, USA). CrP creatinine measurement was by an enzymatic method [23] in all four hospitals as available in the Radiometer ABL800 analysers (Radiometer ABL800 FLEX, Copenhagen, Denmark) located in the ICU departments. For creatinine, the coefficient of variation for the CrC and CrP measurements were 1.4–1.6 % [24] and 0.8–2.0 % [25], respectively.

2.5. Acute kidney injury diagnosis and quantification

AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria using daily serum creatinine data [1]. The occurrence of AKI was determined for every hour that CrC and CrP were collected. Each CrC and CrP was compared to the estimated baseline serum creatinine and the occurrence of AKI and if present, the severity was assessed. The time to AKI diagnosis was calculated from the hour of ICU admission to the hour of the first AKI diagnosis.

As pre-admission serum creatinine was not available in the data set, we estimated baseline serum creatinine using a method previously validated in hospitalised Australian patients with and without CKD where pre-admission creatinine was available for such validation [26,27]. This method utilised the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation and assumed a baseline estimated glomerular filtration rate (eGFR) of 40 mL/min/1.73m^2 and 75 mL/min/1.73m^2 for patients with and without chronic kidney disease, respectively [26]. We performed a sensitivity analysis using the lowest creatinine during ICU admission as the baseline creatinine for determining the diagnosis of AKI.

2.6. Outcomes

The primary outcome was the difference in time to AKI diagnosis calculated as the hour of CrP AKI diagnosis minus the hour of CrC AKI diagnosis. The secondary outcomes were the incidence of AKI and the stage of AKI according to the approach to creatinine measurement.

2.7. Statistical analysis

Descriptive statistics were expressed as frequencies and proportions for categorical variables and medians with interquartile ranges (IQR) or means with standard deviations depending on their parametric or non-parametric distribution. A mixed-effects linear regression model, including the site as a random effect, was developed to examine, which variables were independently associated with the difference in time to AKI diagnosis between CrC and CrP. The variables used for analysis were determined a priori. The results of the multivariable analysis were reported as coefficients with 95 % confidence intervals (95 % CI). A two-sided p-value of <0.05 was chosen to indicate statistical significance. Statistical analyses were performed using R v.4.0.3.

2.8. Ethical considerations

This study was approved by the Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024) with an individual waiver of consent granted.

3. Results

3.1. Patient selection

There were 51,988 adult admissions at the participating sites. Of these, 20,672 patient admission episodes achieved the threshold for arterial blood gas creatinine measurements and 3932 had an AKI diagnosed using CrC during their ICU admission. Of these, 2779 had an ICU length of stay greater than 24 h. In total 1591 patients had two or more POCTs performed in the 24 h before CrC-determined AKI and were included in the analysis.

3.2. Point-of-care testing frequency

Given the non-standardized nature of POCT, the number of POCTs performed in the 24 h before CrC-defined AKI was assessed (Fig. 1). The median number of POCTs performed was 5 (IQR 3–6). Most patients had >6 POCTs (604; 38 %) performed, followed by 2–3 POCTs (552; 35 %) and 4–5 POCTs (435; 22 %).

3.3. Patient characteristics

The patient cohort had a median age of 66 (IQR 53-75) and a median Charlson co-morbidity index of 4 (IQR 2-5). The common reason for admission was cardiovascular (713; 45 %). At the time of admission, the median APACHE 3 score was 67 (IQR 52–85). Over two-thirds of patients were emergency admissions (1099; 69 %). During the ICU admission, most patients required ventilation (1304; 82 %) and vasopressors (1320; 83 %). The median ICU length of stay was 5 days (IQR 3–10) and 189 (12 %) died in ICU. The complete cohort description is presented in **Supplementary Methods Table S3**.

When compared by POCT frequency, patients with more POCT in the 24 h before CrC-defined AKI, were of a similar age and did not have a clinically significant difference in co-morbidity burden or APACHE 3 score. However, those who had a higher number of POCT tests had higher rates of ventilation and higher frequency of vasopressor requirement. In addition, there was an increase in mortality with increased POCT testing frequency.

3.4. AKI characteristics

At the time of AKI diagnosis, the median SOFA score was 8 (6–10), most patients required ventilation (1242; 78 %) and vasopressors (1166; 73 %), and most patients had a stage 1 AKI (843; 53 %). When comparing patients based on the number of POCT tests in the 24 h before CrC-defined AKI, those with more POCTs were more likely to be ventilated and require vasopressors, less likely to require RRT, and had a higher median maximum lactate (Table 1). The trajectory of serum creatinine by the test used first to diagnose AKI until seven days after ICU admission is shown in **Supplementary Methods Fig. S1**, demonstrating that the trajectory of creatinine levels was parallel for all patients with absolute creatinine levels higher in patients diagnosed with CrP.

3.5. Time to AKI diagnosis comparison

The median time of CrC-defined AKI diagnosis was day 1 of ICU (IQR 1-2) and occurred at a median time of 14 h after ICU admission (IQR 9-25) compared to a median day 1 (IQR 1-2) and 7 h (IQR 2-19) after ICU admission for CrP-defined AKI.

The median difference in hours of AKI diagnosis between CrC and CrP was −5 h (−11–−1) (Table 2). The number of POCT tests was associated with the difference in time to AKI diagnosis in hours. As the number of POCT tests increased in the 24 h before CrC-defined AKI diagnosis, the difference in hours increased from −3 (IQR -6 – −1) to −8 (IQR -13–0). The median number of CrC measurements in the 24 h before AKI diagnosis was 1 (IQR 1-2) in all patients. The relationship between the number of POCT tests and the difference in time to AKI diagnosis is demonstrated in Fig. 2. When using the lowest creatinine during ICU admission as the baseline creatinine to diagnosis AKI, the median time of CrC-defined AKI diagnosis was 15 h (IQR 10-29) compared to a median time of 7 h (IQR 2-21) for CrP-defined AKI. The median difference in hours of AKI diagnosis between CrC and CrP in this sensitivity analysis was −6 h (IQR -14-0).

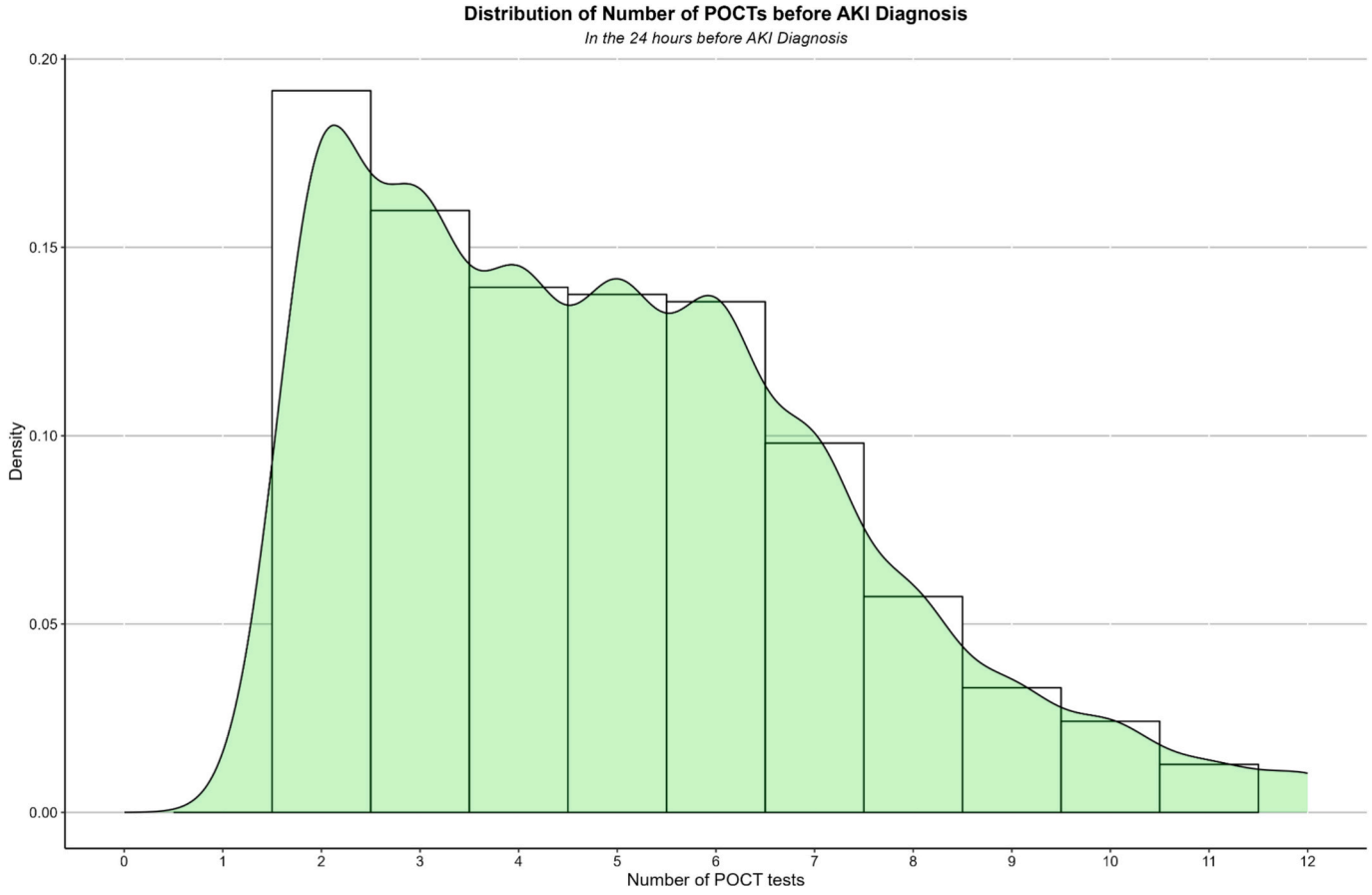

Fig. 1. Distribution of Number of POCTs before AKI Diagnosis.

Table 1
AKI Diagnosis Characteristics by Frequency of POCT Testing.

Variable	Number of POCTs in 24 h before AKI Diagnosis				
	Overall, *N* = 15,91[1]	**2–3**, *N* = 552[1]	**4–5**, *N* = 435[1]	**>6**, *N* = 604[1]	p value[2]
SOFA Score	8 (6, 10)	8 (6, 10)	7 (5, 9)	8 (6, 10)	0.004
Any Ventilation	1242 (78 %)	347 (63 %)	358 (82 %)	537 (89 %)	<0.001
Any Vasopressors	1166 (73 %)	386 (70 %)	315 (72 %)	465 (77 %)	0.023
Maximum Lactate (mmol/L)	2.6 (1.5, 4.8)	2.5 (1.4, 5.3)	2.3 (1.4, 3.9)	2.9 (1.7, 4.9)	<0.001
AKI Stage					<0.001
1	843 (53 %)	241 (44 %)	256 (59 %)	346 (57 %)	
2	314 (20 %)	121 (22 %)	90 (21 %)	103 (17 %)	
3	434 (27 %)	190 (34 %)	89 (20 %)	155 (26 %)	
Any RRT	256 (16 %)	120 (22 %)	49 (11 %)	87 (14 %)	<0.001
Urine Output (mL/day)	829 (379, 1425)	610 (231, 1266)	892 (451, 1466)	909 (499, 1527)	<0.001
Maximum CrC (umol/L)	160 (126, 219)	188 (144, 281)	153 (124, 205)	148 (117, 193)	<0.001
Maximum CrP (umol/L)	186 (145, 263)	207 (148, 310)	177 (137, 238)	183 (145, 248)	<0.001

Abbreviations: AKI = acute kidney injury; CrC = central laboratory creatinine; POCT = point-of-care testing; RRT = renal replacement therapy; SOFA = sequential organ failure assessment.
[1] Median (IQR); n (%).
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test.

Table 2
Timing of AKI Diagnosis by Frequency of POCT Testing.

Variable	Number of POCTs in 24 h before AKI Diagnosis				
	Overall, N = 15,91[1]	**2–3**, N = 552[1]	**4–5**, N = 435[1]	**>6**, *N* = 604[1]	p value[2]
Hour of Diagnosis from CrC [#]	14 (9, 25)	7 (4, 12)	15 (11,21)	20 (15, 37)	<0.001
Hour of Diagnosis from CrP [#]	7 (2, 19)	2 (1, 8)	8 (2, 18)	14 (5, 29)	<0.001
Difference in hours to AKI Diagnosis (CrP - CrC)	-5 (−11,−1)	-3 (−6, −1)	−6 (−11, −1)	−8 (−13,−2)	<0.001
Number of POCTs in 24 h before AKI Diagnosis	5 (3, 6)	2 (2,3)	4 (4, 5)	7 (6, 8)	<0.001
0 to 4 h	2 (1,2)	2 (1, 2)	1 (1, 2)	2 (1, 2)	<0.001
5 to 8 h	1 (1, 2)	1 (0,1)	1 (1, 2)	2 (1, 2)	<0.001
9 to 12 h	1 (1, 2)	1 (0, 1)	1 (1,1)	1 (1, 2)	<0.001
13 to 16 h	1 (1, 2)	0 (0, 1)	1 (0, 1)	1 (1, 2)	<0.001
17 to 20 h	1 (1, 2)	1 (0, 1)	1 (0, 1)	1 (1, 2)	<0.001
21 to 24 h	1 (0,2)	0 (0, 1)	1 (0, 1)	1 (1, 2)	<0.001
Number of CrC measurements in 24 h before AKI Diagnosis	1 (1, 2)	1 (1, 1)	1 (1, 2)	1 (1, 2)	<0.001

The difference in time, days or hours, equals point-of-care creatinine (CrP) derived AKI diagnosis minus central laboratory (CrC) derived AKI diagnosis. A negative difference means that CrP-derived AKI was diagnosed earlier than CrC-derived AKI.
Abbreviations: AKI = acute kidney injury; CrC = central laboratory creatinine; CrP = point-of-care creatinine; POCT = point-of-care testing.
[1] Median (IQR).
[2] Kruskal-Wallis rank sum test.
[#] Time from ICU admission.

Furthermore, the difference in time to diagnosis in hours was influenced by the hour of ICU admission. Thus, patients who were diagnosed with AKI within 24 h of ICU admission had a minimal difference in time to AKI diagnosis between CrP and CrC-defined AKI. However, as demonstrated in **Supplementary Methods Fig. S2**, those patients who were diagnosed at 25–28, 49,72, and > 72 h after ICU admission had a large range of differences in time to AKI diagnosis. In addition, when the time to any increase in the AKI stage was compared between the two methods, POCT delivered earlier diagnosis of worsening AKI across all stages of severity (**Supplementary Methods Fig. S3**).

3.6. Regression analysis

On multivariable regression analysis (**Supplementary Methods Table S4)**, after adjustment for patient characteristics and disease severity, the number of POCTs was independently associated with the difference in time to AKI diagnosis. Thus, when compared to 2–3 POCTs, 4–5 POCTs (OR −3.0; 95 % CI −5.1 - −0.94; $p = 0.004$) and > 6 POCTs (OR −5.4; 95 % CI −7.3 - −3.4; $P < 0.001$) had an increased time difference in AKI diagnosis in favour of POCT. Ventilation during admission was the only other variable independently associated with a difference in time to AKI diagnosis.

3.7. Comparison of CrC Alone to CrP in addition to routine CrC

The maximum AKI stage during ICU admission was compared in the entire cohort by the methods of creatinine measurement where CrC alone was compared to the use of both CrC and CrP (Fig. 3). The use of both CrC and CrP achieved an increased number of patients classified as stage 2 and stage 3 AKI (346 (22 %) vs 294 (185) and 702 (44 %) vs 667 (42 %), respectively; $p = 0.003$).

Furthermore, the detection of deteriorating renal function was determined by considering every increase in the AKI stage during the entire ICU admission, where each patient may experience multiple increases in the AKI stage (Supplementary Methods **Fig. S4**). When comparing the use of both CrC and CrP to CrC alone, there was a significant increase in the detection of an increase in AKI severity (5139 vs 3899; $p \leq 0.001$). When comparing the use of both CrC and CrP to CrC alone, the combination of methods detected more increases in AKI severity to each AKI stage (stage 1: 1767 (34 %) vs 1.170 (30 %); stage 2: 1.301 (25 %) vs 809 (21 %) and stage 3: 2071 (40 %) vs 1920 (49 %); $p < 0.001$). A sensitivity analysis, excluding the RRT from the definition of stage 3 AKI, demonstrated similar findings with increased frequency of AKI detection across all AKI stages (Supplementary Methods **Fig. S5**).

4. Discussion

4.1. Key findings

We analysed the incidence and timing of AKI in 1591 critically ill patients who had POCT combined with routine central laboratory measurement of serum creatinine and compared it with routine central laboratory creatinine measurement alone.

First, we found that the frequency of POCT varied significantly across the patient population. Second, we found that patients with more POCT measurements had higher severity of illness and were more likely to require invasive therapies. Third, in patients with two or more POCTs per day, AKI was detected significantly earlier than with CrC. Fourth, we found that more frequent POCT was associated with earlier CrP diagnosed AKI compared with CrC. Fifth, more POCTs were independently

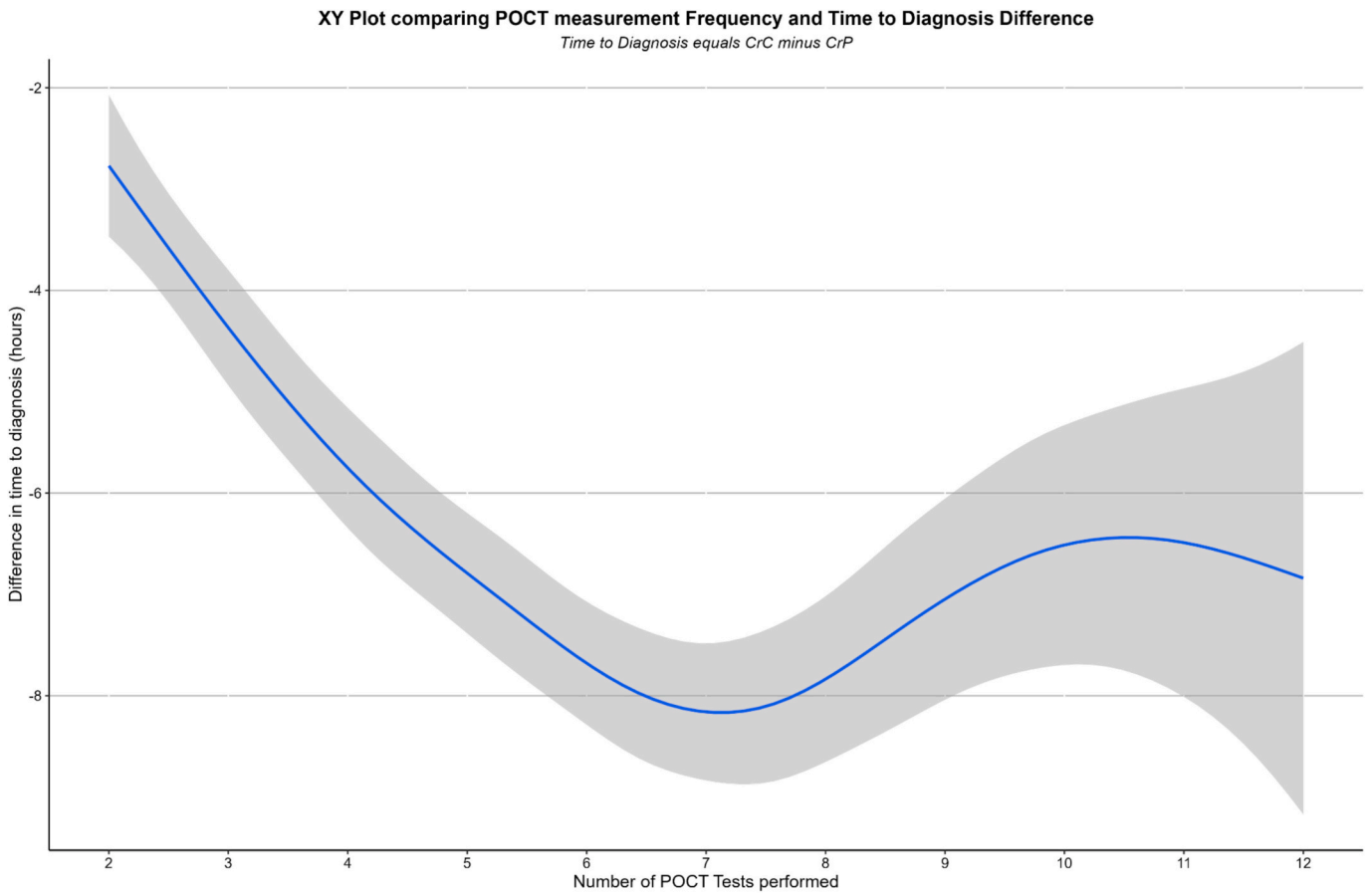

Fig. 2. XY Plot comparing POCT measurement frequency and Time to Diagnosis Difference.

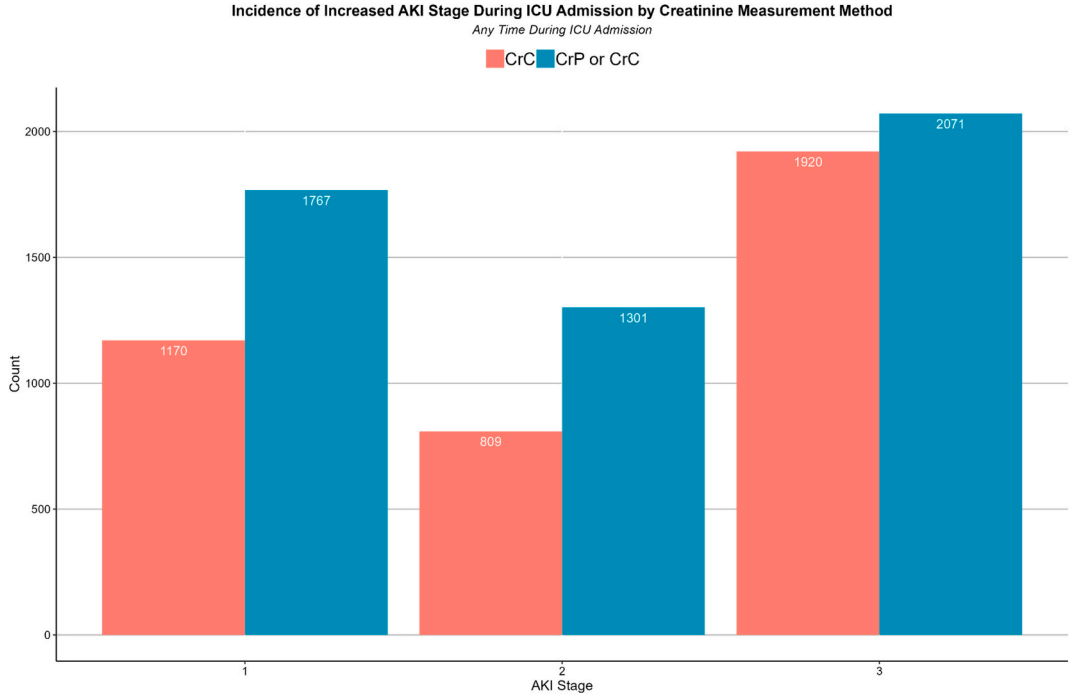

Fig. 3. Incidence of Increased AKI Stage During ICU Admission by Creatinine Measurement Method.
This figure demonstrates that when considering all episodes of deterioration in renal function, or worsening AKI stage, the use of both CrC and CrP detects more AKI at each AKI stage.

associated with a shorter time to AKI diagnosis after adjustments for patient characteristics and disease severity. Finally, when comparing the use of CrC alone to the use of both CrC and CrP in the entire cohort, the combined use of both CrC and CrP was associated with more frequent diagnosis of AKI across all stages.

4.2. Relationship to literature

No study has compared the incidence and timing of AKI between the combination of routine CrC and CrP testing vs routine CrC alone. In the critically ill population, research examining CrP has been very limited in nature. Previous research has examined the relationship, or correlation, between CrP and CrC, demonstrating a high level of correlation and concordance in critically ill patients [3,28]. Furthermore, previous research has examined how fluctuations in CrP relate to the risk of developing AKI diagnosed with CrC. Such research demonstrated that even small increases in CrP are associated with the subsequent development of CrC-defined AKI [29,30]. Thus, our results present novel information on the diagnostic impact of CrP in critically ill patients.

4.3. Implications of study findings

Our findings imply that the use of CrP can facilitate the earlier detection of creatinine-defined AKI than with CrC alone. As logical, the magnitude of the difference in time to detect AKI between CrC and CrP was related to the frequency of POCT. Thus, our results suggest that frequent use of CrP can diagnose AKI up to 20 h earlier. Such earlier detection of both AKI and, by association, clinical deterioration might lead to earlier intervention and, perhaps, better outcomes. [31] Furthermore, the use of CrP and CrC, when compared to CrC alone, resulted in more detection of stage 2 and stage 3 AKI. Such detection of more severe AKI could potentially impact epidemiology and prognostication. Given that CrP is provided as part of routine ABG testing within the ICU, incorporating CrP into the diagnosis and management of AKI would require no changes to current care processes and no increase in resource utilisation.

4.4. Strengths and limitations

Our study has several strengths. First, the cohort was sampled from several large tertiary ICUs, which provide care to a wide range of critical care patients, enhancing the study results' external validity. Second, the data was extracted directly from the ICU electronic medical record used at all sites and contained all creatinine measurements, CrC and CrP, minimising ascertainment and selection bias. Third, the granularity of the data allowed for the hourly detection of AKI, thereby allowing for the detection of small but potentially clinically significant differences not previously possible.

We acknowledge some limitations. First, this is an observational study with inherent limitations. Therefore, no direct causal inferences can be drawn from the findings, and the associations demonstrated are hypothesis-generating only. Second, the frequency of POCT was determined by the treating clinicians or patient survival and, as demonstrated in our results, related to the severity of the illness. Therefore, the early detection of AKI with CrP may not apply to patients who did not have frequent POCT testing and would not be possible in patients who die before developing an AKI. Third, for simplicity and clarity, we defined AKI using creatinine only and did not consider urine output defined AKI. Though this limits the general applicability of the study, it facilitated the direct comparison of CrP and CrC, thereby allowing the detection of differences in time to diagnosis. Future research will be required to determine the role of CrP when urine output-defined AKI is also considered and its potential value as a trigger for kidney protective interventions such as earlier removal of nephrotoxins, adjustment of drug dosage, or optimisation of hemodynamics. Fourth, interference from medications and other biochemical variables may impact the measurement of creatinine differently between methods. However, recent research in nearly 80,000 paired samples from almost 20,000 critically ill patients demonstrated a mean difference of 0.40 mmol/L between POCT and central lab testing, providing robust evidence of equivalence. [3] Fifth, the aetiology of AKI could not be inferred from the available data. Therefore, heterogeneity of AKI may result in differential time to AKI diagnosis with POCT. Lastly, estimating baseline creatinine is complex and may result in misclassification of AKI. [32] However, we utilised validated equations and performed a sensitivity analysis utilising an alternative 'baseline creatinine' estimation, which did not demonstrate any difference in the outcome.

5. Conclusion

In this study of critically ill patients who had POCT testing for serum creatinine, CrP combined with routine CrC resulted in the diagnosis of AKI up to 20 h earlier than CrC alone. The magnitude of the difference in the time to diagnosis was related to the frequency of POCT testing, with more frequent POCT associated with an earlier detection of AKI by CrP. Furthermore, when comparing the use of CrC alone to the use of combined CrC and CrP in the entire cohort, the combined use CrC and CrP was associated with greater detection of AKI of all stages during the ICU admission. These findings suggest the need to investigate the impact of combined CrP and CrC on the timing and effect of interventions directed at protecting the kidney from injury in the setting of critical illness.

Statement of ethics

This study was approved by the Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024) with an individual waiver of consent granted.

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Authors contribution

The study conception and design (KW, RB); data acquisition (all authors); analysis (KW); interpretation of data (all authors); article drafting (KW, RB), article revision for important intellectual content (all authors); final approval of the version submitted for publication (all authors); agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (KW, RB).

CRediT authorship contribution statement

Kyle C. White: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jason Meyer:** Writing – review & editing, Data curation, Conceptualization. **Kevin B. Laupland:** Writing – review & editing, Data curation, Conceptualization. **Siva Senthuran:** Writing – review & editing, Data curation, Conceptualization. **Kiran Shekar:** Writing – review & editing, Data curation, Conceptualization. **James McCullough:** Writing – review & editing, Data curation, Conceptualization. **Rinaldo Bellomo:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2025.155050.

Data availability statement

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data released for research under Sect. 280 of the Public Health Act 2005 requires an application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

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