

# Acute kidney injury following resection of hepatocellular carcinoma: prognostic value of the acute kidney injury network criteria

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**Background:** Acute kidney injury (AKI) is associated with increased morbidity and mortality after liver resection. Patients with hepatocellular carcinoma (HCC) have a higher risk of AKI owing to the underlying association between hepatic and renal dysfunction. Use of the Acute Kidney Injury Network (AKIN) diagnostic criteria is recommended for patients with cirrhosis, but remains poorly studied following liver resection. We compared the prognostic value of the AKIN creatinine and urine output criteria in terms of postoperative outcomes following liver resection for HCC.

**Methods:** All patients who underwent a liver resection for HCC from January 2010 to June 2016 were included. We used AKIN urine output and creatinine criteria to assess for AKI within 48 hours of surgery.

**Results:** Eighty liver resections were performed during the study period. Cirrhosis was confirmed in 80%. Median hospital stay was 9 (interquartile range 7–12) days, and 30-day mortality was 2.5%. The incidence of AKI was higher based on the urine output than on the creatinine criterion (53.8% v. 20%), and was associated with prolonged hospitalization and 30-day postoperative mortality when defined by serum creatinine (hospital stay: 11.2 v. 20.1 d,  $p = 0.01$ ; mortality: 12.5% v. 0%,  $p < 0.01$ ), but not urine output (hospital stay: 15.6 v. 10 d,  $p = 0.05$ ; mortality: 2.3% v. 2.7%,  $p > 0.99$ ).

**Conclusion:** The urine output criterion resulted in an overestimation of AKI and compromised the prognostic value of AKIN criteria. Revision may be required to account for the exacerbated physiologic postoperative reduction in urine output in patients with HCC.

**Contexte :** L'insuffisance rénale aiguë (IRA) est associée à une morbidité et à une mortalité accrues après une résection hépatique. Les patients atteints d'un carcinome hépatocellulaire (CHC) sont exposés à un risque plus grand d'IRA en raison du lien sous-jacent entre l'insuffisance hépatique et l'insuffisance rénale. Les critères diagnostiques de l'Acute Kidney Injury Network (AKIN) sont recommandés chez les patients cirrhotiques, mais ils n'ont pas été bien étudiés dans les cas de résection hépatique. Nous avons comparé la valeur pronostique des critères de l'AKIN tels que la créatinine et le débit urinaire pour ce qui est des résultats postopératoires suite à une résection hépatique pour CHC.

**Méthodes :** Tous les patients soumis à une résection hépatique pour CHC entre janvier 2010 et juin 2016 ont été inclus. Nous avons utilisé les critères de l'AKIN concernant le débit urinaire et la créatinine pour évaluer l'IRA dans les 48 heures suivant la chirurgie.

**Résultats :** Quarante-vingt résections hépatiques ont été effectuées pendant la période de l'étude. La cirrhose a été confirmée dans 80 % des cas. Le séjour hospitalier médian a duré 9 jours (intervalle interquartile 7–12 jours) et la mortalité à 30 jours a été de 2,5 %. L'incidence de l'IRA a été plus élevée selon le critère débit urinaire que selon le critère créatinine (53,8 % c. 20 %), et a été associée à un séjour plus long et à une mortalité à 30 jours plus élevée suite à l'intervention selon le critère créatinine sérique (séjour hospitalier : 11,2 c. 20,1 j,  $p = 0,01$ ; mortalité : 12,5 % c. 0 %,  $p < 0,01$ ), mais non selon le critère débit urinaire (séjour hospitalier : 15,6 c. 10 j,  $p = 0,05$ ; mortalité : 2,3 % c. 2,7 %,  $p > 0,99$ ).

**Conclusion :** Le critère débit urinaire a donné lieu à une surestimation de l'IRA et a réduit la valeur pronostique des critères de l'AKIN. Une révision serait peut-être nécessaire pour tenir compte de la réduction physiologique plus marquée du débit urinaire en période postopératoire chez les patients atteints d'un CHC.

Postoperative acute kidney injury (AKI) is reported in approximately 15% of patients undergoing liver resections, and is associated with increased morbidity and mortality.<sup>1-3</sup> Multiple predisposing factors have been described, but the most common mechanism is acute tubular necrosis secondary to perioperative hypovolemia and hypotension.<sup>4</sup> The diagnosis of AKI has been poorly defined, with variable biochemical and urine output diagnostic criteria.<sup>7-10</sup> These continued inconsistencies prompted a consensus definition of AKI by the Acute Dialysis Quality Initiative in 2004 (RIFLE criteria; i.e., risk, injury, failure, loss of kidney function, and end-stage kidney disease).<sup>11</sup> These criteria were then revised in 2007 (Acute Kidney Injury Network [AKIN] criteria).<sup>12</sup> While the accuracy and prognostic value of this classification system has been confirmed in critically ill patients, their applicability in patients following hepatic resection is unclear.

Patients with cirrhosis represent a particularly high-risk subgroup for AKI. Although the mechanism of AKI within this context is not completely elucidated, most believe reduced effective blood volume due to splanchnic and peripheral vasodilation leads to systemic hypoperfusion and compensatory production of antidiuretic hormone. This subsequently promotes activation of the renin-angiotensin-aldosterone and sympathetic nervous systems.<sup>4</sup> Not surprisingly, renal hypoperfusion and impaired excretion of water and sodium prevail, which subsequently exacerbates a reduction in urine output combined with a postsurgical inflammatory and hormonal response.

During the last 2 decades, widespread use of low central venous pressure (CVP) during liver transection has raised additional concerns regarding a possible increase in morbidity due to renal hypoperfusion. Low CVP is used during hepatic resection to reduce backflow bleeding from the suprahepatic venous system. This technique has proven effective in reducing blood loss and the need for blood transfusion as well as morbidity associated with hemorrhagic shock during resection.<sup>5</sup> A recent retrospective study demonstrated that AKI had only a transient and limited clinical impact on 2116 patients who underwent low CVP-assisted hepatectomies.<sup>6</sup> Postoperative AKI, defined by an increase in serum creatinine, was diagnosed in 350 (16%) patients, with clinically relevant AKI and oliguria developing in only 9 of them.

Unfortunately, the impact of underlying cirrhosis in exacerbating AKI and the postoperative oliguric response remains unknown. Furthermore, the relevant clinical prognostic utility of both biochemical and urine output criteria for AKI, has not been defined previously within the literature. As a result, the objective of this study was to compare the prognostic value of creatinine and urine output within the AKIN criteria in terms of postoperative outcomes following liver resection for HCC.

## METHODS

### *Population, study design and setting*

Patients undergoing hepatic resection for HCC from January 2010 to June 2016 at the Foothills Medical Centre (FMC), in Calgary, Alta., Canada, were included. This centre is the tertiary care referral centre for all hepatic diseases among a population of nearly 3 million citizens within Southern Alberta.

Perioperative care remained constant during the study period and used the standard practice of low CVP status during liver resection based on both pre- and intraoperative fluid restriction as well as the occasional use of diuretics and vasopressors. Parenchymal transection was conducted using a hybrid saline-bipolar energy instrument. Portal inflow occlusion was not routinely required. Fluid resuscitation to re-establish normovolemia was initiated immediately following removal of the specimen and ensuring adequate hemostasis. Postoperative assessment and treatment of low urine output and hypotension were conducted by the anesthesiologist in the post-anesthesia care unit. Patients were then transferred to a high-observation postoperative care suite on the surgery ward, and ongoing concerns and interventions were communicated to the hepatobiliary surgery fellow.

### *Definition of acute postoperative acute renal failure*

Acute kidney injury was defined within 48 hours after surgery according to AKIN criteria:<sup>10</sup>

- urine output < 0.5 mL/kg/h for 6 hours, or
- relative (1.5 times) or absolute ( $\geq 0.3$  mg/dL or  $\geq 26.5$   $\mu$ mol/L) increase in baseline serum creatinine value.

### *Data collection and outcome measures*

We collected data retrospectively from preoperative assessment clinic notes, operative and pathology reports, and postoperative vital signs and fluid balance flow sheets. Serum creatinine values were obtained at 3 am on postoperative days 1 and 2. Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula.<sup>13</sup>

### *Statistical analysis*

Variables were summarized as proportions and medians with interquartile ranges (IQR). The 2-sample *t* test was used to compare continuous variables. Incidence of AKI within 48 hours after surgery as well as its association with hospital length of stay were determined for AKIN urine output and serum creatinine criteria. All statistical analyses were conducted using SPSS software, version 19, and results were considered significant at  $p < 0.05$ .

## RESULTS

### Demographics and baseline clinical characteristics

A total of 80 liver resections were performed during the study period. Patient demographic and clinical characteristics were typical for hepatic resections at this centre (Table 1).

Median baseline eGFR was 87.6 (IQR 71.7–114.3) mL/min. Most patients (83.8%) had a preoperative diagnosis of underlying liver disease, most commonly secondary to viral hepatitis (Table 2). Other comorbidities included hypertension ( $n = 28$ , 35.0%), diabetes ( $n = 20$ , 25.0%) and coronary artery disease ( $n = 10$ , 12.5%).

### Surgery and postoperative outcomes

Minor hepatic resections were performed in 61 (76.2%) patients; 13 were laparoscopic. Major resections were all open and included 16 right, 1 extended right, 1 left and 1 extended left hepatectomy. Median estimated blood loss was 200 (IQR 100–337) mL for minor and 600 (IQR 300–800) mL for major resections. Inflow occlusion was used during 15 (18.8%) resections, for an average of 15 (IQR 11–20) minutes. Background fibrosis/cirrhosis was identified within the pathology specimen in 64 (80.0%) patients (Table 3).

The median hospital stay was 9 (IQR 7–12) days, and 6 (7.5%) patients were readmitted within 30 days from discharge. Major complications (Clavien–Dindo classification  $\geq 3$ ) occurred in 16 (20.0%) patients. The most common major complications were liver failure ( $n = 5$ ), intra-

abdominal abscess ( $n = 5$ ), pneumonia ( $n = 4$ ), hemorrhage ( $n = 3$ ) and bile leak ( $n = 2$ ). Eight (10.0%) patients were admitted to the intensive care unit for a median duration of 10 (IQR 3–13) days. Thirty-day mortality was 2.5% and resulted from liver failure in association with hemorrhage after a minor hepatectomy ( $n = 1$ ), and pneumonia complicated with empyema after a hemihepatectomy ( $n = 1$ ).

### Acute kidney injury and postoperative outcomes

The incidence of AKI was 20% (16 of 80 patients) based on creatinine and 53.8% (43 of 80 patients) based on urine output criteria.

Acute kidney injury was associated with a prolonged hospital stay and increased 30-day mortality when defined by serum creatinine elevation (hospital length of stay: 20.1 d v. 11.2 d,  $p = 0.01$ ; mortality: 12.5% v. 0%,  $p < 0.01$ ), but not by urine output (hospital length-of-stay: 15.6 d v. 10 d,  $p = 0.05$ ; mortality: 2.3% v. 2.7%,  $p > 0.99$ ).

Odds of major postoperative morbidity (Clavien–Dindo classification  $\geq 3$ ) was at least 3 times as high in the subgroup of patients with AKI regardless of the diagnostic criteria used. This association, however, reached statistical

**Table 1. Demographic and baseline clinical characteristics**

Characteristic	No. (%) of patients*
Age, yr; median (IQR)	62 (54–70)
Sex	
Male	61 (76.2)
Female	19 (23.8)
BMI, median (IQR)	25.6 (23.1–29.3)
ASA classification	
1	6 (7.5)
2	48 (60.0)
3	24 (30.0)
Unknown	2 (2.5)
Hypertension	28 (35.0)
Diabetes	20 (25.0)
Coronary artery disease	10 (12.5)
Underlying liver disease	67 (83.8)
Estimated glomerular filtration rate; mL/min	
$\geq 90$	36 (45.0)
60–89	30 (37.5)
30–59	14 (17.5)
ASA = American Society of Anesthesiologists; BMI = body mass index; IQR = interquartile range.	
*Unless specified otherwise.	

**Table 2. Underlying liver disease**

Etiology	No. (%) of patients
Hepatitis B	28 (41.8)
Hepatitis C	19 (28.4)
Alcohol	6 (9.0)
Alcohol + hepatitis B or C	6 (9.0)
NAFLD	4 (6.0)
Hemochromatosis	3 (4.5)
Unknown	1 (1.5)
Child classification	
A	66 (98.5)
B	1 (1.5)
NAFLD = non-alcoholic fatty liver disease.	

**Table 3. Operative and postoperative characteristics**

Characteristic	No. (%) of patients*
Liver resection	
Minor ( $\leq 2$ segments)	60 (75.0)
Major	20 (25.0)
Estimated blood loss, mL; median (IQR)	250 (100–500)
Inflow occlusion	15 (18.8)
Duration, min; median (IQR)	15 (11–20)
Cirrhosis on pathology	64 (80.0)
Tumor size, cm; median (IQR)	4 (2.3–7)
Hospital length-of-stay, d; median (IQR)	9 (7–12)
Major postoperative complications (Clavien–Dindo $\geq 3$ )	16 (20.0)
30-day mortality	2 (2.5)
IQR = interquartile range.	
*Unless specified otherwise.	

significance only in the subgroup defined by urine output elevation (urine output: odds ratio [OR] 4.8, 95% confidence interval [CI] 1.2–18.4,  $p = 0.02$ ; creatinine: OR 3.1, 95% CI 0.9–10.7,  $p = 0.08$ ).

Regression analyses of postoperative AKI according to creatinine or urine output are shown in Table 4.

**DISCUSSION**

To our knowledge, this is the first study to evaluate the effectiveness of the AKIN criteria in defining postoperative AKI following hepatic resection for HCC. The high prevalence of underlying cirrhosis, concurrent poor physiologic reserve, and increased morbidity and mortality associated with this diagnosis necessitates a distinct evaluation of the AKIN diagnostic criteria among patients with HCC. The results of this study indicate a lower prognostic value of AKIN urine output criterion compared with the creatinine criterion for clinically relevant postoperative outcomes.

The RIFLE criteria were initially published in 2004<sup>11</sup> and stratified AKI into 3 levels of renal dysfunction. These included kidney risk, injury and/or failure, and were based on relative increases in serum creatinine values or glomerular filtration rates (GFR) as well as urine output. Two clinical outcome categories were also used to describe renal failure persisting for more than 4 weeks: loss and end-stage renal disease. The AKIN classification was subsequently published in 2007<sup>12</sup> as an update to the RIFLE criteria. Renal dysfunction categories were renamed as stages 1, 2 and 3, and the 2 clinical outcome groups were excluded. Using absolute increases in creatinine values was recommended to replace changes in GFR in an attempt to minimize variability on

the estimation and interpretation of GFR.<sup>14</sup> Based on associated adverse outcomes, a diagnostic threshold increase as small as 0.3 mg/dL in blood creatinine was proposed to define AKI.<sup>15</sup>

Several studies have evaluated the accuracy and application of the RIFLE and AKIN criteria in critically ill<sup>16–18</sup> and cardiac patients.<sup>19–21</sup> These evaluations have produced mixed results; some favoured the RIFLE<sup>20</sup> or AKIN criteria,<sup>21</sup> whereas others found no real advantage to either classification system.<sup>16,22</sup> In patients with cirrhosis, a correlation of AKIN with mortality has been documented,<sup>23,24</sup> and the International Ascites Club and the Acute Dialysis Quality Initiative have recommended its use over the RIFLE criteria.<sup>25</sup> Unfortunately, the applicability of AKIN criteria is often hindered by a lack of baseline creatinine measurements and/or adequate urine output monitoring.<sup>26</sup> Despite the retrospective design of our study, these limitations were absent because the preoperative assessment of renal function as well as monitoring of postoperative creatinine levels and urine output are routinely performed for all patients. Mean urine output per hour was calculated based on total 8-hour shift volume, instead of the recommended hourly assessment. The importance of this common adaptation of the AKIN criteria in overestimating AKI is still poorly characterized.

In this study, baseline renal function was reported in terms of Cockcroft–Gault estimates of creatinine clearance. The Cockcroft–Gault regression equation is a popular practical approach to predict creatinine clearance based on the patient’s age, sex and weight. It was originally described in 1976 by Dr. Donald W. Cockcroft, a third-year general medicine resident working with Dr. Matthew H. Gault at the Queen Mary Veterans’

**Table 4. Univariate and multivariate analysis of predictive factors for postoperative acute kidney injury according to creatinine output and urine output criteria**

Factor	Univariate analysis, creatinine criterion*		Multivariate analysis, creatinine criterion*		Univariate analysis, urine output criterion†	
	OR	<i>p</i> value	OR (95%CI)	<i>p</i> value	OR (95%CI)	<i>p</i> value
Age	1.07	0.03	1.10 (1.02–1.19)	0.02	1.03 (1.00–1.07)	0.20
Sex	1.62	0.51	—	—	0.41 (0.14–1.17)	0.12
BMI ≥ 30	2.78	0.14	—	—	3.90 (1.00–15.25)	0.07
ASA ≥ 3	1.47	0.55	—	—	2.32 (0.85–6.33)	0.14
Hypertension	4.07	0.19	—	—	1.67 (0.65–4.29)	0.35
Diabetes	2.93	0.11	—	—	1.14 (0.41–3.17)	> 0.99
Coronary artery disease	1.81	0.42	—	—	0.89 (0.24–3.35)	> 0.99
Preoperative eGFR < 60 mL/min	2.78	0.14	—	—	1.70 (0.53–5.45)	0.39
Cirrhosis	0.51	0.45	—	—	1.24 (0.39–3.95)	0.77
Surgery (minor v. major)	4.33	0.02	1.87 (0.37–9.45)	0.45	4.89 (1.46–16.36)	< 0.01
Laparoscopic	0.29	0.45	—	—	0.48 (0.14–1.61)	0.24
Pringle	1.65	0.48	—	—	2.84 (0.81–9.92)	0.15
EBL	1.003	< 0.01	1.002 (1.000–1.005)	0.07	1.001 (1.000–1.003)	0.18

ASA = American Society of Anesthesiologists; BMI = body mass index; CI = confidence interval; EBL = estimated blood loss; eGFR = estimated glomerular filtration rate; OR = odds ratio.

\*Relative (1.5 times) or absolute (≥ 0.3 mg/dL or ≥ 26.5 μmol/L) increase in baseline serum creatinine value.

†Mean 8-h urine output < 0.5 mL/kg/h.

Hospital in Montreal. This method had limited use for patients with cirrhosis, obesity, or low serum creatinine levels; and it also presented an overall tendency to overestimate GFR. A variety of formulas have been proposed to improve estimation accuracy, but these usually involve more complex equations with a more restricted application to specific subsets of patients. In our study, eGFR was reported only to characterize baseline renal function, and it was not used to assess interval changes or to define AKI.

The AKIN recommendation to exclude reversible causes of renal dysfunction, such as volume depletion, clearly applies to the low-CVP liver resection scenario. More specifically, low urine output in the first few postoperative hours is generally responsive to intravenous hydration within a prompt timeframe. This recommendation was also addressed within our data set by considering urine output data only after appropriate postoperative fluid resuscitation was completed (i.e., the patients were discharged from the post-anesthesia care unit).

It became clear that the incidence of posthepatic resection AKI was significantly higher than that reported in previous series comprising noncirrhotic patients.<sup>1,3,6,27</sup> This increase was largely in patients with isolated low urine output and was not associated with a prolonged hospital stay. Similar findings with RIFLE classification have been reported in nonsurgical series.<sup>28,29</sup> The urine output criterion has been reported to be more inclusive and less predictive of mortality, whereas the creatinine criterion selects more severely ill patients.<sup>30</sup> The association of both parameters, however, has been demonstrated to be a superior predictor of mortality in the intensive care unit.<sup>31</sup> More recently, AKI defined by creatinine criteria was reported as the strongest independent predictor of postoperative mortality in a series of 457 patients with HCC.<sup>32</sup> Unfortunately, the predictive value of urine output criteria was not investigated.

Unlike findings in the critically ill population, our findings suggest that a revision of the urine output diagnostic threshold for postoperative AKI should be considered following liver resection for HCC. Multiple factors, including intraoperative fluid restriction, acute inflammatory and hormonal response to surgical trauma, and the high prevalence of underlying cirrhosis, conspire to create an exacerbated postoperative physiologic oliguric response. Furthermore, the adequacy of postoperative intravenous hydration in this setting might not be reliably monitored via typical urine output parameters. This is particularly concerning since excessive administration of intravenous fluids has been associated with prolonged ileus, increased morbidity and longer hospital stay after abdominal surgery.<sup>33–35</sup> More precisely, avoidance of volume and sodium overload is supported by “grade A” evidence in

current protocols for enhanced recovery after surgery.<sup>36</sup> This is particularly concerning in the context of a baseline tendency of patients with cirrhosis to retain water and sodium, which in turn can aggravate postresection liver dysfunction. Goal-directed fluid therapy has been recommended, but specific urine output parameters should be considered for patients with cirrhosis undergoing liver resection.

As a more immediate clinical application, this study intends to inform the current development of AKI alerting systems. Implementation of AKI alerting systems is growing, and our regional health authority’s (Alberta Health Services) Surgery and Kidney Strategic Clinical Networks have considered AKI identification to be a priority for clinical quality improvement.

### Limitations

Our study has some limitations. First, it represents a retrospective analysis of the experience in a single centre. Second, despite the central role of cirrhosis within this data set, our patient population was defined by the diagnosis of HCC. This inclusion trigger is justified by the often limited objective assessment of cirrhosis in the preoperative period as well as the prevalent coexistence of background cirrhosis in patients with HCC. It also reflects a more pragmatic study approach in accordance with our plan to develop an identification system for posthepatic resection AKI in patients with HCC. Finally, significance of regression analyses of postoperative AKI was limited by the small study population. For the same reason, subgroup analyses of AKIN stages 1 to 3 were not performed.

### CONCLUSION

The AKIN urine output criterion resulted in an overestimation of AKI incidence after liver resection for HCC, which compromises the prognostic value of AKIN criteria with regard to hospital length of stay and postoperative mortality. Revision of the AKIN criteria to account for the physiologic postoperative reduction in urine output should be considered for patients with HCC undergoing low-CVP hepatic resections.

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**Competing interests:** None declared.

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