Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy

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Abstract

Background. Radical nephrectomy is a significant risk factor for chronic kidney disease (CKD). There are few reports on the renal outcome of acute kidney injury (AKI) after radical nephrectomy. The aim of this study was to determine the incidence of AKI and whether post-operative AKI is associated with new-onset CKD after radical nephrectomy for renal cell cancer (RCC).

Methods. We conducted a retrospective study of 519 adult patients (>40 years old) with normal renal function who underwent unilateral radical nephrectomy for a solitary renal cortical tumour and were pathologically diagnosed with RCC between January 2000 and February 2007. Post-operative AKI was classed using risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria. CKD was defined as a decrease in estimated glomerular filtration rate (GFR) to <60 mL/min/1.73 m².

Results. According to the RIFLE criteria, 165 of 175 patients fell into the AKI risk category, 8 patients fell into the AKI injury category and 2 patients fell into the AKI failure category. Multivariate analysis revealed that older age [odds ratio (OR) 1.02, 95% confidence interval (CI) 1.00–1.05], male gender (OR 3.13, 95% CI 1.91–5.12), higher body mass index (OR 1.08, 95% CI 1.01–1.15), smaller RCC size (OR 0.87, 95% CI 0.81–0.93) and higher preoperative GFR (OR 1.04, 95% CI 1.03–1.06) were independent risk factors for post-operative AKI. CKD was more prevalent in the AKI risk group than in patients without AKI 1 year after surgery (54.7% versus 43.9%, respectively; P = 0.006) and 3 years after surgery (50% versus 32%, respectively; P = 0.003). Patients who experienced post-operative AKI had a 4.24-fold higher risk of new-onset CKD after multiple adjustments were made to the data (95% CI 2.28–7.89, P < 0.001).

Conclusion. AKI after radical nephrectomy in patients with RCC is a potent risk factor for new-onset CKD. Prevention of post-operative AKI is essential for reducing the incidence of CKD after nephrectomy.

Keywords: acute kidney injury; chronic kidney disease; radical nephrectomy; renal cell carcinoma

Introduction

Chronic kidney disease (CKD) has become a worldwide public health problem, and its prevalence is rising. Currently, it affects ~10% of adults in the USA [1]. CKD has been reported to be a major risk factor for cardiovascular disease and has a graded association with the risk of hospitalization and mortality from any cause [2, 3]. Even mild impairments of renal function are associated with an increased risk of mortality [2, 3].

Radical nephrectomy has been the standard treatment for localized renal cell cancer (RCC) for many years [4]. However, some retrospective series have reported that the incidence of CKD after radical nephrectomy is as high as 65% [5, 6]. Thus, renal functional preservation is an important consideration in management of renal tumours. The incidence of small renal masses increased owing to the widespread use of advanced abdominal imaging [7–9]. It highlights the importance of the nephron-sparing approach.

The loss of a functioning renal mass after nephrectomy induces compensatory renal growth [10–12]. Adaptive renal hypertrophy occurs immediately after nephrectomy and the decrease in glomerular filtration rate (GFR) thereafter is transient and subclinical [13, 14]. However, some nephrectomy patients experience clinically evident acute kidney injury (AKI). There is limited information on AKI after radical nephrectomy.

This retrospective study evaluated the incidence of AKI and determined whether post-operative AKI is associated with new-onset CKD after radical nephrectomy for RCC.
Materials and methods

Patients

Between January 2000 and February 2007, 638 adult patients (>40 years old) who underwent unilateral radical nephrectomy for a solitary renal cortical tumour and were pathologically diagnosed with renal cell carcinoma were identified using the electronic databases of the Samsung Medical Centre, Seoul, Korea. We excluded patients with a preoperative GFR <60 mL/min/1.73 m² (n = 56), insufficient data (n = 46) or a single functioning kidney (n = 1). We also excluded patients who underwent subsequent treatment that could affect renal function post-operatively: additional nephrectomy (n = 3), thermal ablation of a kidney (n = 6) and treatment with potentially nephrotoxic chemotherapeutic agents such as cisplatin (n = 7). Data from 519 patients were analysed in this study. All patients had a normal contralateral kidney on preoperative assessment. The study was approved by the Institutional Review Board of the hospital.

Clinical data and laboratory investigations

Preoperative characteristics including [age, sex, body mass index (BMI), serum creatinine concentration, estimated GFR, diabetes mellitus and hypertension] were extracted from medical records and an electronic database. Estimated GFRs were calculated with the abbreviated Modification of Diet and Renal Disease (MDRD) Study equation [15]. The equation is: GFR = 186 × (serum creatinine)⁻¹.154 × (age)⁻⁰.²⁰⁵, from which the result is multiplied by 0.742 for female patients. Calibrated serum creatinine values were used.

Hypertension was defined as a systolic blood pressure >140 mmHg, a diastolic blood pressure >90 mmHg or self-reported hypertension with or without ongoing pharmacologic treatment. Diabetes mellitus was defined as a history of type 1 or type 2 diabetes mellitus treated pharmacologically without ongoing pharmacologic treatment. Diabetes mellitus was defined as a decrease in estimated GFR to <60 mL/min/1.73 m² and was defined as the longest single dimension of the lesion.

The main predictor was the occurrence of post-operative AKI, which was defined according to the risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria as follows [16]: (i) risk: 1.5-fold increase in the serum creatinine level, (ii) injury: 2-fold increase in serum creatinine level, (iii) failure: 3-fold increase in serum creatinine level. We did not consider the urine output criteria. To assess the occurrence of AKI, the highest serum creatinine level within 7 days of the nephrectomy was compared with the preoperative serum creatinine level. To evaluate the renal outcome of post-operative AKI, serum creatinine levels at 3 months, 12 ± 3 months and 36 ± 3 months after the nephrectomy were recorded for all patients. CKD was defined as a decrease in estimated GFR to <60 mL/min/1.73 m² [17].

In our centre, patients who underwent radical nephrectomy were released from hospital at post-operative Day 7 ± 1 if they did not have post-operative complications. Serum creatinine level was measured every other day during hospitalization. Patients were encouraged to visit outpatient clinics after their discharge and to submit samples for measurement of serum creatinine level 1 and 3 months post-operatively and every 3 months thereafter until 3 years after the radical nephrectomy.

Statistical analysis

Data were expressed as the median and inter-quartile range. Univariate and multivariate logistic regression analyses were used to identify predictors of post-operative AKI. Multivariate analysis included age, sex and variables with a P-value of <0.1 according to univariate analyses. Wilcoxon signed-rank tests were performed to compare GFRs and creatinine values at different times. The chi-square test was used to compare the frequencies of CKD 1 and 3 years after nephrectomy according to post-operative AKI grade. We also used logistic regression analyses to investigate whether post-operative AKI was associated with CKD 3 years after radical nephrectomy. We regarded P-values <0.05 as significant. All statistical analyses were done using SPSS 12.0 (SPSS Inc., Chicago, IL).

Results

Table 1. Patient characteristics at the time of surgery and cancer size

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (N = 519)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 (49–64)</td>
</tr>
<tr>
<td>Gender, male N (%)</td>
<td>368 (70.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.5 (22.6–26.3)</td>
</tr>
<tr>
<td>Hypertension N (%)</td>
<td>223 (43.0)</td>
</tr>
<tr>
<td>Diabetes mellitus N (%)</td>
<td>52 (10.0)</td>
</tr>
<tr>
<td>Pathologic size of RCC (cm)</td>
<td>5.0 (3.5–7.5)</td>
</tr>
<tr>
<td>Preoperative creatinine (mg/dL)</td>
<td>0.9 (0.8–1.1)</td>
</tr>
<tr>
<td>Preoperative GFR (mL/min/1.73 m²)</td>
<td>60–89 N (%)</td>
</tr>
<tr>
<td>≥90 N (%)</td>
<td>343 (66.3)</td>
</tr>
<tr>
<td>Histology (postsurgery)</td>
<td>175 (33.7)</td>
</tr>
<tr>
<td>Conventional clear cell N (%)</td>
<td>431 (83)</td>
</tr>
<tr>
<td>Papillary N (%)</td>
<td>28 (5.4)</td>
</tr>
<tr>
<td>Chromophobe N (%)</td>
<td>26 (5.0)</td>
</tr>
<tr>
<td>Oncocytoma N (%)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Others N (%)</td>
<td>33 (6.4)</td>
</tr>
</tbody>
</table>

AData are median (IQR) or number (%).

| Other covariates included cystic, mixed, sarcomatoid, unclassified and granular types.

Table 2. Logistic regression models of AKI after nephrectomy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>1.04</td>
<td>0.86–1.26</td>
</tr>
<tr>
<td>Male (versus female)</td>
<td>2.92</td>
<td>1.84–4.63</td>
</tr>
<tr>
<td>BMI (per 2 kg/m²)</td>
<td>1.12</td>
<td>0.99–1.27</td>
</tr>
<tr>
<td>HTN (versus no)</td>
<td>0.96</td>
<td>0.66–1.39</td>
</tr>
<tr>
<td>DM (versus no)</td>
<td>1.64</td>
<td>0.92–2.94</td>
</tr>
<tr>
<td>Size of RCC (per 1 cm)</td>
<td>0.86</td>
<td>0.80–0.92</td>
</tr>
<tr>
<td>Preoperative GFR (per 10 mL/min/1.73 m²)</td>
<td>1.37</td>
<td>1.20–1.57</td>
</tr>
</tbody>
</table>

AKI after radical nephrectomy

AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; DMRC, Modification of Diet and Renal Disease; GFR, glomerular filtration rate; HTN, hypertension; MDRD, Modification of Diet and Renal Disease; OR, odds ratio; P-values, probability values; RFR, risk failure rate; RCC, renal cell carcinoma; RIFLE, risk, injury, failure, loss, end-stage kidney disease; UN, uncontrolled.
without AKI \((n = 344)\), the median GFR decreased from 81 mL/min/1.73 m² before surgery to 61 mL/min/1.73 m² immediately after surgery \((P < 0.001)\) and did not change thereafter \((60 \text{ mL/min}/1.73 \text{ m}^2 \text{ at 3 months after nephrectomy and 62 mL/min/1.73 m}^2 \text{ 1 year after nephrectomy})\). In the AKI risk group \((n = 148)\), the median GFR decreased from 86 mL/min/1.73 m² before surgery to 51 mL/min/1.73 m² immediately after surgery \((P < 0.001)\). The median GFR then increased to 55 mL/min/1.73 m² at 3 months after surgery and 58 mL/min/1.73 m² 1 year after surgery \((P < 0.001)\). GFRs 1 year after the operation were lower in the AKI risk group than in patients without AKI \((P = 0.024)\). The AKI injury and AKI failure groups \((n = 10)\) demonstrated changes in GFR similar to those of the AKI risk group. Figure 2 shows the prevalence of CKD 1 and 3 years after nephrectomy according to post-operative AKI grade. One year after nephrectomy, CKD was more prevalent in the AKI risk group than in patients without AKI \((54.7\% \text{ versus } 43.9\%, \text{ respectively}; \ P = 0.006)\); this difference was also evident 3 years after surgery \((50\% \text{ versus } 32\%, \text{ respectively}; \ P = 0.003)\).

Next, we conducted logistic regression analyses to determine whether post-operative AKI was associated with CKD 3 years after radical nephrectomy. Patients who experienced post-operative AKI had a 4.24-fold higher risk of new-onset CKD after multiple adjustments were made to the data \((95\% \text{ CI } 2.28–7.89, \ P < 0.001)\) (Table 3).

Discussion

This study showed that 33.7% of patients who underwent radical nephrectomy experienced post-operative AKI. Older age, male sex, high BMI, high preoperative GFR and small RCC size were identified as independent risk factors for post-operative AKI. One year after surgery, median GFR was lower in the AKI group than in patients without AKI. Patients who experienced post-operative AKI had a 4.24-fold higher risk of new-onset CKD after radical nephrectomy.

There is little published information on AKI after radical nephrectomy for RCC. There is some data on changes in renal function and serum creatinine level after donor nephrectomy [12, 14, 18]. It has been shown that unilateral nephrectomy in patients with two normally functioning kidneys results in compensatory hypertrophy of the remaining kidney [12, 14, 18]. Serum creatinine level usually increases to 20% above baseline but remains within the normal range [19, 20]. Although the incidences of AKI as defined by RIFLE criteria were not reported in previous studies on donor nephrectomies, the overall increment of serum creatinine level in those studies was lower than in our cohort [19, 20]. Serum creatinine level increased to 50% above baseline after nephrectomy in one-third of our study subjects. The immediate change in serum creatinine level after nephrectomy may reflect compensation by the remaining kidney. Differences in post-operative changes in serum creatinine level between donor nephrectomy and our radical nephrectomy for RCC may have been caused by subject characteristics. Kidney donors are younger and have less comorbidity than patients with RCC [20, 21]. The incidence of AKI increased consistently with age in our study. However, we did not measure the degree of adaptive hyperfiltration of the remaining kidney after nephrectomy.

Older age, male sex, high BMI, high preoperative GFR and small RCC size were identified as risk factors for post-operative AKI. It remains unclear whether all of these factors are associated with less and slower compensation of the remaining kidney. There is no consensus regarding clinical predictors of adaptive hyperfiltration [10, 14]. Anderson et al. [14] demonstrated that the degree of compensatory hypertrophy was greater in male and in young patients. Research aimed at defining clinical characteristics associated with adaptive hyperfiltration is needed to reduce the incidence of CKD after radical nephrectomy.

It is interesting that high preoperative GFR and small RCC size were associated with a high risk of AKI. Our cohort was composed entirely of subjects with normal renal function. Among subjects with normal renal function, a high GFR may reflect abnormal hyperfiltration. In such cases, a sudden reduction in the number of functioning nephrons may result in a lesser degree of adaptive hypertrophy. It has been stated that compensatory renal enlargement may occur even before nephrectomy in patients with contralateral RCC [11]. Based on this finding, adaptive hypertrophy of the unaffected kidney of patients with a large RCC might have occurred at the time of the nephrectomy; hypertrophy after nephrectomy would be relatively...
less in patients with a large RCC than in those with small RCC. Measurements of individual kidney GFRs pre- and post-nephrectomy are needed to prove this assumption.

In our study, 135 of 354 (38%) patients developed new-onset CKD 3 years after unilateral radical nephrectomy. This incidence is lower than that of previous reports [5, 6]. As our study excluded patients with pre-existing CKD and who underwent subsequent treatment with agents that are potentially nephrotoxic, the incidence of CKD in our cohort might have been lower than that in entire RCC patients undergoing radical nephrectomy.

Complete surgical excision by partial nephrectomy has now become a standard of care for small renal masses (<4 cm), based on compelling data demonstrating that radical nephrectomy is associated with an increased risk of CKD [22, 23]. However, radical nephrectomy is still a viable option when the tumour size or location is such that the surgeon considers partial nephrectomy unfeasible [22].

In our centre, 769 cases of radical and partial nephrectomy were performed during the study period, between January 2000 and February 2007. Among 350 cases of small renal tumours (<4 cm), 226 cases (64.6%) took radical nephrectomy. Several reports have identified risk factors for CKD after radical nephrectomy [5, 6]. Jeon et al. [5] reported that age, preoperative GFR and diabetes were associated with the development of CKD. Huang et al. [6] reported that old age and low preoperative GFR were risk factors for CKD. Additionally, our data revealed that post-operative AKI was associated with a 4.24-fold higher risk of new-onset CKD after radical nephrectomy.

Recent studies have shown that AKI increases the risk of CKD and end-stage renal disease [24–26]. The underlying mechanism by which AKI causes progressive CKD is not completely understood. However, experimental works have shown that renal parenchymal injury sustained during episodes of AKI may result in permanent tubule-interstitial fibrosis and a reduction in the number of functioning nephrons [27–29]. Furthermore, AKI may lead to permanent damage to the renal microvasculature and trigger inflammatory and fibrotic signalling pathways [30, 31]. In the case of radical nephrectomy for RCC, the response of the remaining kidney after loss of a functioning renal mass may affect the development of AKI and CKD.

Bijol et al. [32] reported that 60% of cases of tumour nephrectomy specimens had evident pathologic abnormalities in non-neoplastic parenchyma and suggested the presence of underlying medical renal disease can be a risk factor for progressive renal disease after nephrectomy. We evaluated non-neoplastic histology in 31 cases (18 cases in the AKI group and 13 cases in the non-AKI group, randomly selected from each group, data not shown). None were found to have specific pathologic findings. Although 31 cases might not be enough to draw a conclusion, we assumed that underlying medical renal disease was not frequent in our subjects. Subject characteristics can, at least in part, explain this apparent difference. Our subjects had estimated GFR ≥60 mL/min/1.73 m² preoperatively and showed low comorbidity (diabetes 10%). Even though

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### Table 3. Logistic regression models of new-onset CKD at 3 years after nephrectomy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>2.52 (1.93–3.31)</td>
<td>1.89 (1.39–2.57)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male (versus female)</td>
<td>1.38 (0.86–2.21)</td>
<td>0.95 (0.53–1.71)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (per 2 kg/m²)</td>
<td>1.15 (0.98–1.35)</td>
<td>1.06 (0.87–1.29)</td>
<td>NS</td>
</tr>
<tr>
<td>HTN (versus no)</td>
<td>1.82 (1.18–2.81)</td>
<td>1.14 (0.65–1.98)</td>
<td>NS</td>
</tr>
<tr>
<td>DM (versus no)</td>
<td>2.85 (1.40–5.79)</td>
<td>2.74 (1.07–6.98)</td>
<td>0.035</td>
</tr>
<tr>
<td>Size of RCC (per 1 cm)</td>
<td>0.94 (0.87–1.01)</td>
<td>0.97 (0.89–1.07)</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative GFR (per 10 mL/min/1.73 m²)</td>
<td>0.53 (0.43–0.65)</td>
<td>0.47 (0.36–0.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Post-operative AKI</td>
<td>2.18 (1.39–3.43)</td>
<td>4.24 (2.28–7.89)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HTN, hypertension; DM, diabetes mellitus. Multivariate analysis included age, gender, BMI, DM, hypertension, size of RCC, preoperative GFR and post-operative AKI.

One hundred and sixty-five patients were excluded from this analysis because 3-year GFRs were not available.
there was no evident pathology, 61% showed moderate arteriolar sclerosis (defined as an intimal thickening up to the thickness of the media or a luminal loss of 50%) and 29% showed partial tubular atrophy (>1% of evaluated area). When we evaluated the association between non-neoplastic histology and clinical outcomes, the severity of arteriolar sclerosis and the degree of tubular atrophy did not differ according to AKI occurrence or the development of CKD. Even in the study of Bijol et al. [32], the severity of arteriolar sclerosis in patients with normal renal parenchyma did not significantly affect the renal outcome. Additional studies on the clinical significance of arteriolar sclerosis and tubular atrophy found in patients with normal renal parenchyma are needed.

Our study had some limitations. First, it has the inherent weaknesses of all studies with a retrospective design, including the use of data from past medical records. Second, about one-third of patients were lost to follow-up within 3 years after surgery. However, the proportion of missing data did not differ between the AKI group and the group without AKI. Third, we were unable to measure new-onset diabetes and new-onset hypertension during follow-up. However, renal complications of hypertension and diabetes mellitus do not become clinically overt within 3 years. Fourth, we used estimated GFR by the abbreviated MDRD study equation to assess kidney function. It has been widely used in various clinical studies. However, some investigators have suggested that the MDRD equation underestimates GFR in healthy subjects without kidney disease [33, 34].

In conclusion, post-operative AKI in patients with RCC is a potent risk factor for new-onset CKD after radical nephrectomy. This result contributes towards a novel insight into renal prognosis of post-operative AKI after radical nephrectomy. Prevention of post-operative AKI is essential to limit the incidence of CKD after nephrectomy. Fourth, we used estimated GFR by the abbreviated MDRD study equation to assess kidney function. It has been widely used in various clinical studies. However, some investigators have suggested that the MDRD equation underestimates GFR in healthy subjects without kidney disease [33, 34].

In conclusion, post-operative AKI in patients with RCC is a potent risk factor for new-onset CKD after radical nephrectomy. This result contributes towards a novel insight into renal prognosis of post-operative AKI after radical nephrectomy. Prevention of post-operative AKI is essential to limit the incidence of CKD after nephrectomy. Thus, additional studies are warranted to define high-risk groups and to establish effective preventive strategies for AKI after radical nephrectomy.

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Conflict of interest statement. None declared.

References

Acute kidney injury in patients admitted to a liver intensive therapy unit with paracetamol-induced hepatotoxicity

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Abstract

Background. Paracetamol overdose can cause acute kidney injury (AKI) independent of its hepatotoxic effects. We aimed to determine the prevalence of AKI (AKI Network definition) in those with paracetamol-induced hepatotoxicity, identify factors associated with development, assess impact on the outcomes of patient survival and length of stay and determine the proportion of patients recovering renal function (estimated glomerular filtration rate > 60 mL/min) by the time of hospital discharge or transfer out.

Methods. Between 2000 and 2007, patients admitted to a tertiary referral liver intensive therapy unit (LITU) with paracetamol-induced hepatotoxicity were identified from a prospectively maintained database and evaluated.

Results. Those receiving a liver transplant were excluded (n = 54), leaving 302 patients. Renal function remained normal in 21%, the remainder developing AKI (Stages 1–8%, 2–6% and 3–65%). Vasopressor requirement, mechanical ventilation, higher admission phosphate and lower sodium levels along with a higher Day 3 lactate and lower haematocrit were associated with AKI. In survivors with AKI, 51% had recovery of renal function, while 7% remained dialysis dependant although none required it chronically. Overall, there was 25% mortality, all having Stage 3 AKI but AKI was only a univariate not multivariate predictor of reduced patient survival. AKI independently predicted longer length of stay.

Conclusions. AKI is very common in critically ill patients with paracetamol-induced hepatotoxicity requiring LITU admission. Although outcomes are poorer with AKI than with normal renal function, they are better than those found in other intensive therapy unit populations. Gradual recovery of renal function is seen in all patients.

Keywords: acute liver failure; acute renal failure; hepatotoxicity; intensive therapy unit; paracetamol;

Introduction

Acute kidney injury (AKI) occurs in 40–80% of patients with acute liver failure (ALF) [1, 2]. The underlying aetiology is frequently multifactorial and AKI may occur as a consequence of sepsis, hypovolaemia-induced renal hypoperfusion, hepatorenal syndrome, intra-abdominal hypertension or there may be a common underlying cause for the hepatic and renal toxicity including drugs, such as paracetamol [3, 4].

Paracetamol is a commonly used analgesic and paracetamol-induced hepatotoxicity remains the most common aetiology of ALF in the UK and USA [5, 6]. Hepatotoxicity, defined as an aspartate aminotransferase level of >1000 IU/L, following intentional or unintentional ingestion of paracetamol is observed in 3–26% of patients, depending on the factors including time to presentation for treatment with N-acetylcysteine [7, 8]. ALF (hepatotoxicity in the presence of encephalopathy and coagulopathy), however, is relatively rare.

Acute renal impairment occurs in 2–10% of patients who ingest excessive amounts of paracetamol. It has also been noted in the absence of hepatotoxicity [9–12]. Although renal biopsy is rarely undertaken in patients with AKI, a pattern of acute tubular injury due to toxic metabolites (N-acetyl-p-benzoquinone-imine) generated by primarily liver-derived cytochrome P450 enzymes has been