Acute Kidney Dysfunction in Patients with Chronic Hepatitis C Virus Infection: Analysis of Viral and Non-viral Factors

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Background: Multiple studies have shown a relationship between chronic hepatitis C infection and chronic kidney disease. The prevalence, severity, underlying etiologies and predictors of acute kidney dysfunction (AKD) events in patients with hepatitis C has not been studied. **Methods:** We investigated viral and non-viral factors in the development renal dysfunction in 468 HCV patients retrospectively over a period of observation ranging from 3 months to 6 yrs. **Results:** A total of 124 AKD events occurred in 63 patients. On regression analysis; gender, race, alcohol abuse, HIV (Human immune deficiency virus) status, body mass index, baseline viral load (HCV-PCR), and genotype did not predict an event of AKD. Decompensated liver disease, history of IVDU, diabetes mellitus and baseline creatinine were independent predictors of AKD. **Conclusion:** Development of AKD in patient with hepatitis C virus infection is independent of the genotype and viral load at baseline and is mostly predisposed by known prevalent factors in patients with hepatitis C such as diabetes, hypertension and intravenous drug use. Decompensated liver disease is the single most viral-related factor that predisposes for AKD. (J CLIN EXP HEPATOL 2014;4:8–13)

Hepatitis C virus is estimated to infect 4 million people in the United States and 100 million people worldwide. It is transmitted primarily through exposure to blood products and intravenous drug use. Chronic infection occurs in 85%–90% of persons exposed to the virus and may progress to chronic active hepatitis and cirrhosis.¹ In addition to liver disease, HCV infection has been associated with a wide variety of extra-hepatic manifestations, including mixed cryoglobulinemias and renal involvement.²

The propensity for renal involvement and the high prevalence of reported comorbid conditions like diabetes mellitus and HIV infections may put patients with chronic HCV infection at elevated risk of AKD, especially in the setting of acute illness and multiple organ failure. The Acute Dialysis Quality Initiative (ADQI) Group published a consensus definition (the RIFLE criteria) for acute renal failure. RIFLE defines 5 grades of severity: risk (class R), injury (class I), failure (class F), loss (class L), end stage disease (E).³

Keywords: acute renal failure, acute kidney dysfunction, hepatitis C virus, cirrhosis, end stage renal disease

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Abbreviations: ADQI: acute dialysis quality initiative; AKD: acute kidney dysfunction; IVDU: intravenous drug use; ESRD: end stage renal disease; HCV: hepatitis C virus; LVP: large volume paracentesis

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We systematically studied the overall prevalence, underlying clinical causes, predictors and prognosis and AKD in a large cohort of HCV infected patients using the RIFLE criteria.

METHODS

Study Population

Consecutive patients seen at the outpatient gastroenterology and hepatology clinic of the Metropolitan Hospital Center of New York Medical College between Jan 2004 and Jan 2005 were enrolled into this study. Study data include all institutionally available electronic patient records (available since June 1999) and standardized medical record reviews. Data were reviewed for evidence of acute kidney dysfunction based on serial creatinine measurements. Baseline was defined as the first visit available in the electronic record of these patients. Follow up data of renal functions were reviewed until June 2006. Patients were excluded if they did not have at least 2 measures of serum creatinine within a 3 month period from the baseline serum creatinine. Of the 551 patients 468 subjects fulfilled the enrollment criteria. Eighty patients were excluded due to lack of follow up data of the serum creatinine and 3 patients were excluded due to chronic dialysis at baseline.

Measurements

We defined acute kidney dysfunction using RIFLE criteria³ in order to identify mild to severe cases of AKD in a large cohort of ambulatory patients.

AKD was defined as an increase in serum creatinine based on the RIFLE criteria (during at least 2 days). In view of the requirement of serial creatinine measurement of at least 2 days to satisfy the definition of AKD, all subjects required to have an admission in the hospital to be eligible to be defined as having AKD. The first and second authors (SKS, CL) reviewed all AKD events. Recovery patterns of renal failure were defined as complete, partial or worsening. Complete when renal functions returned to the baseline, partial when there is incomplete improvement from the peak value of creatinine achieved during the an acute event of AKD and worsening when there is worsening renal function or no consistent improvement at 1 month follow up.

The number of episodes of AKD was recorded by reviewing the electronic data system using serial serum creatinine levels. Underlying clinical conditions at the time of the AKD events were reviewed in order to determine potential causes of the AKD. Renal survival, defined as time to develop ESRD, was recoded at 30 days and 3 months when available.

Co-morbidities Definitions and Laboratory Data

All laboratory data were retrieved from the medical and electronic chart review of the New York Medical College; Metropolitan Hospital Center central data system. Hepatitis C virus sero-status was based on hepatitis C antibody and/or detectable HCV-RNA (RT-PCR) (Quest diagnostics, USA). HCV genotypes were recorded whenever available. Serial serum creatinine measurements were available from June 1999 in our hospital electronic data system.

Co-morbidities such as systemic chronic hypertension and diabetes mellitus were defined based on the medication review and review of the medical chart. Other co-variables recorded were age, race, sex, previous AIDS-defining clinical condition and history of intravenous drug use (IVDU).

The study was performed in accordance to the institutional ethical committee guideline and policies.

Statistical Analysis

Descriptive statistics for patients were reported. Continuous variables were summarized as means $\pm$ SD or percentages, as appropriate. Group comparisons were made by Mann Whitney test for continuous data. Chi-Square test (with Yates correction if indicated) and Fishers exact tests were used for nominal or categorical data. Both univariate and multivariate logistic regression analysis were conducted with acute renal failure as the dependent variable; age, gender, race, a history of alcohol abuse, positive HIV status, BMI, baseline viral load (HCV-PCR) baseline serum creatinine, history of IVDU, presence of diabetes mellitus, hypertension, presence of decompensated liver disease, having received treatment with interferon as co-variables. A *p*-value of <0.05 was used to indicate statistical

significance. Cox regression analysis was performed to analyze the recovery of renal function following an event of AKD. All analyses were performed using the SPSS statistical package version (SPSS, Chicago, IL version 17).

RESULTS

Baseline Characteristics and Demographics

Of the 468 patients included in the present study 310 (66.2%) were male, with a mean age of 50.46 ± 10.5 . There was no significant difference in the gender distribution of patients with and without AKD (Table 1). Patients with AKD were significantly older (55.6 ± 10 vs. 49.6 ± 10.4 , $P < 0.0001$). Although the majority of the population included in the study were either black 125 (26.7%) or Hispanic 300 (64.1%), no significant racial differences were noted in patients with and without AKD among blacks, Hispanics and white populations (Table 1). Mean BMI was comparable among these groups. Advanced liver disease and cirrhosis were present in 15 (3.2%) patients, 12 (19%) patients who experienced AKD, compared to 3 (0.7%) without any AKD events ($P < 0.05$).

Patients with AKD have significantly higher prevalence of comorbid conditions like diabetes mellitus (47.6% vs. 16.5%, $P < 0.0001$), and hypertension (69.8% vs. 38.8%, $P = 0.0005$). Thirty of the 97 (31%) diabetic patients compared to only 33 of the 371 (8.9%) non-diabetic patients had an event of AKD ($P < 0.0001$). Also a higher number of patients with AKD were noted to have HIV positive status, although this did not reach statistical significance (22.5% vs. 12.6%, $P = 0.08$). A history of intravenous drug abuse was noted to be significantly commoner in patients with chronic HCV infection with AKD (44.4% vs. 29.42, $P = 0.01$).

Baseline viral load (HCV-PCR) did not differ between the patients with and without AKD (5.58 ± 0.48 vs. 5.57 ± 0.38 , $P = 0.5$). However, of the 147 patients who were ever treated with an interferon based regimen, only 55 patients completed the scheduled duration of treatment regimen, 31 of the 55 (56.4%) had sustained virological response. No significant differences were noted in the prevalence of AKD in patients who completed the scheduled duration of therapy and achieved SVR compared to those who did not attain SVR [4/31 (12.9%) vs. 1/24 (4.1%), $P = 0.37$]. Decompensated liver disease was noted in 12 patients with AKD (19%) as compared to only 3 (0.7%) decompensated liver disease patients without AKD episodes ($P < 0.0001$). No significant difference was noted in the distribution of any predominant genotype in patients with AKD.

Prevalence of Acute Kidney Dysfunction

Of the 468 patients with chronic HCV infection 63 patients experienced 124 episodes of AKD events over a period of follow up ranging from 3 months to 6 years. Based on

Table 1 Clinical Characteristics and Demographic Profile.

	All patients (N = 468)	AKD (N = 63)	Without AKD (N = 405)	P value
Male (%)	310 (66.2)	46 (73)	264 (65.2)	0.22
Age years (Mean +/– SD)	50.46 ± 10.5	55.6 ± 10	49.6 ± 10.4	<0.05
Race numbers (%)				
Black	125 (26.7)	18 (28.6)	107 (26.4)	0.72
Hispanic	300 (64.1)	45 (71.4)	255 (63.4)	0.19
White	18 (3.8)	0 (0)	18 (4.4)	0.15
Others	24 (5.3)	0 (0)	25 (6.2)	0.03
BMI	28.3 ± 6.2	28.6 ± 5.6	28.2 ± 6.4	0.46
Hypertension number (%)	201 (42.9)	44 (69.8)	157 (38.8)	<0.05
Diabetes mellitus number (%)	97 (20.7)	30 (47.6)	67 (16.5)	0.06
HIV number (%)	40 (8.5)	9 (14.3)	31 (7.7)	0.08
IVDU number (%)	147 (31.4)	28 (44.4)	119 (29.4)	0.02
History of Etoh abuse number (%)	81 (17.3)	10 (15.9)	71 (17.5)	0.75
Interferon ever Number (%)	144 (30.8)	11 (17.5)	133 (32.8)	0.01
Decompensated liver disease	15 (3.2)	12 (19)	3 (0.7)	<0.05
Base line Serum Cr. (Mean +/– SD)	0.9 ± 0.3	1.18 ± 0.7	0.9 ± 0.24	<0.05
Base line Serum Cr. = > 1.2	49 (10.5)	18 (28.6)	31 (7.7)	<0.05
Base line Serum Cr < 1.2 (later developing CKD)	18 (4.3%)	8 (17.8%)	10 (2.7%)	<0.05
HCV-PCR (Log Copies/ml × 10 ⁵)	5.57 ± 0.4	5.58 ± 0.48	5.57 ± 0.38	0.5
Genotype distribution:				
HCV genotype 1	262 (56%)	31 (49.2)	231 (57)	0.24
HCV genotype 2	42 (9%)	9 (14.3)	33 (8.1%)	0.11
HCV genotype 3	14 (3%)	1 (1.6%)	13 (3.2)	0.48
HCV genotype 4	10 (2.1%)	1 (1.6%)	9 (2.2)	0.83
Mixed genotype Type (1 and 2)	4 (0.9%)	–	4 (1)	–
Genotyping: not available	136 (29.1%)	21 (33.3)	115 (28.4%)	0.42

RIFLE criteria, 58 (46.8%) were at risk, 20 (16.1%) had injury, 44 (35.5%) had failure, 2 (1.6%) were classified under category “loss” among these patients, respectively. Most possible predisposing factors for AKD are shown in Table 2. Nausea, vomiting, diarrhea, dehydration, and/or large volume paracentesis were responsible for the major bulk of the AKD events accounting for 27 of the 124 (21.8%) events. 22 (17.7%) AKD events were related to infections, mostly due to sepsis/bacteremia, spontaneous bacterial peritonitis, pneumonia, and rarely due to isolated causes like urinary tract infections, pyelonephritis, acute cholecystitis. Gastrointestinal bleeding (*N* = 9) was associated with 7.3% of the AKD events. At least 8 (6.5%) patients had hepatic encephalopathy which may have indirectly affected development of AKD.

Predictors of Acute Renal Failure

Binary logistic regression analysis revealed baseline serum creatinine, history of IVDU, presence of diabetes mellitus,

hypertension, presence of decompensated liver disease and higher age were significant predictors of AKD events, and having received treatment with interferon ever was a negative predictor of AKD. Gender, race, a history of alcohol abuse, positive HIV status, BMI and baseline viral load (HCV-PCR) did not predict an event of AKD in patients with chronic HCV infection (Table 4). On multivariate regression analysis, only decompensated liver disease, history of IVDU, diabetes mellitus and baseline serum creatinine were independent positive predictors of developing AKD (Table 5).

Prognosis in Patients with Acute Kidney Dysfunction

Prognosis was assessed in terms of recovery of renal function, development of CKD, ESRD (End stage renal disease), and in hospital mortality.

Of the 124 events of AKD, 68 (54.8%) recovered completely and their serum creatinine returned to the

Table 2 Predisposing Factors of Acute Kidney Dysfunction in HCV Infected Patients.

Predisposing factors	Frequency (%) ^{a,b}
Nausea, Vomiting, Diarrhea, Dehydration, LVP	27 (21.8)
Hypotension	7 (5.6)
Infection related	22 (17.7)
• Sepsis	13 (10.5)
• SBP	3 (2.4)
• Pneumonia	3 (2.4)
• UTI	1 (0.8)
• Acute cholecystitis	1 (0.8)
• Pyelonephritis	1 (0.8)
GI bleed	9 (7.3)
Hepatic encephalopathy	8 (6.5)
Diuretic induced	6 (4.8)
Diabetic ketoacidosis	3 (2.4)
Congestive heart failure	2 (1.6)
Hepato-renal syndrome	2 (1.6)
Uncontrolled hypertension	1 (0.8)
Drug induced	4 (3.2)
AGN	1 (0.8)
Contrast induced nephropathy	3 (2.4)
Nephrotic syndrome	2 (1.6)
Rhabdomyolysis	5 (4)
Urethral stricture	2 (1.6)
Undetermined	20 (16.1)

^aFrequency events was calculated based on 124 ARF events in 63 Chronic HCV infected patients.

^bThe etiologies of ARF events ($n = 124$) although segregated as isolated events as shown above, multiple etiologies were responsible in a number of cases. The dominant etiology was assigned as the inciting event.

baseline, whereas 43 (34%) had partial recovery defined as reduction in the peak creatinine value but not reaching the baseline. Thirteen (10.5%) of the AKD events actually had a worsening of their baseline serum creatinine, and progressed to either CKD or ESRD. Serum creatinine measured prior to an episode of AKD was less than 1.2 in 72 of the 124 (58%) noted AKD events (Table 3). Of

Table 3 Comparison of the Patterns of Recovery Following an Episode of AKD (N = 124) Based on Pre-failure Serum Creatinine Level.

	Serum Cr < 1.2 (N = 72)	Serum Cr $\geq$ 1.2 (N = 52)	
Complete recovery	53 (73.6)	15 (28.8)	<0.05
Partial recovery	14 (19.4)	29 (55.8)	<0.05
Worsening	5 (6.9)	8 (15.4)	0.13

Table 4 Predictors of AKD in Patients with Chronic HCV Infection.

	R	Sig.	Odds ratio	95% C.I. for Odds ratio	
				Lower	Upper
Male Sex	0.37	0.22	1.44	0.80	2.61
Age (yrs)	0.05	0.00	1.06	1.03	1.08
Race hispanic	0.38	0.19	1.47	0.82	2.63
Race black	0.11	0.72	1.11	0.62	2.01
History of alcohol abuse	-0.12	0.75	0.89	0.43	1.83
History of IVDU	0.65	0.02	1.92	1.12	3.30
Diabetes mellitus	1.52	0.00	4.59	2.62	8.02
Hypertension	1.30	0.00	3.66	2.06	6.49
Positive HIV status	0.70	0.08	2.01	0.91	4.45
HCV-PCR (log cps/ml)	0.07	0.85	1.07	0.51	2.28
HCV Genotype 1 (vs. others)	-0.31	0.24	0.73	0.43	1.24
Base line S. Cr	1.77	0.00	5.83	2.64	13.16
Decompensated liver disease	3.45	0.00	31.53	8.61	115.49
Treatment with IFN ever	-8.84	0.07	0.43	0.22	0.86
BMI	0.01	0.68	1.01	0.96	1.06

Note: White race was not analyzed as predictor in view of small sample size.

the 52 (42%) AKD events where in a higher serum creatinine (≥ 1.2) was noted at baseline, mean recovery time was prolonged (18.57 ± 11.18 vs. 15.24 ± 9.21 days, $P = 0.080$). Cox-Regression analysis based on baseline serum creatinine (< 1.2 vs. ≥ 1.2) revealed a distinctly prolonged recovery pattern in patients with an AKD event

Table 5 Predictors of AKD in Patients with Chronic HCV Infection (Multivariate Regression Analysis).

	R	Sig.	Odds ratio	95% C.I. for Odds ratio	
				Lower	Upper
Age (yrs)	0.02	0.23	1.02	0.99	1.06
Decompensated liver disease	3.21	0.00	24.72	5.74	106.47
Treatment with IFN ever	-0.34	0.38	0.71	0.33	1.52
History of IVDU	0.99	0.00	2.70	1.37	5.33
Diabetes mellitus	1.11	0.00	3.04	1.49	6.20
Hypertension	0.68	0.07	1.97	0.94	4.12
Positive HIV status	0.46	0.35	1.59	0.59	4.26
Base line S. Cr	1.85	0.00	6.39	2.59	15.76

Figure 1 Shows the cumulative recovery pattern based on the baseline serum creatinine levels (S. Cr).

with higher serum creatinine prior to the AKD events ($P < 0.0001$, OR: 3.409, 95% CI: 1.912–6.079; [Figure 1](#)). Also, a higher peak level of serum creatinine was associated with a more prolonged recovery time ([Figure 2](#)). Mean duration of recovery in Gr1, 2 and 3 are 13.07 ± 7.07 days, 18.83 ± 10.53 days, and 22.33 ± 13.15 days respectively.

Of the 63 patients with AKD, 18 patients had S. Cr < 1.2 at the baseline who later developed CKD, 8 (17.8%) had

Figure 2 Shows the cumulative recovery pattern based on the peak serum creatinine levels (S. Cr).

recurrent episodes of AKD compared to 10 (2.7%) without an episode of AKD ($P < 0.05$). ESRD was noted in 15 of the 468 HCV patients, 4 of the 405 patients without a history of AKD events compared to 11 (17.5%) who had a prior episode of AKD ($P < 0.05$). Significant proportion of the patients who progressed to ESRD had DM [5 of 15 (33.3%)] and had hypertension [10 of 15 (66.7%)], again highlighting the importance of these underlying co-morbidities in the development of AKD events in patients with chronic hepatitis C.

DISCUSSION

In this large retrospective analysis of 468 patients with chronic HCV, 63 patients experienced with 124 episodes of AKD. The study highlighted the fact that viral-related factors likely do not play any significant role in the causation of AKD events, and known non-viral factors are the sole determinants in predisposing AKD events in hepatitis C infected patients. However patients with advanced liver disease are more likely to develop AKD events. Acute volume depletion secondary to nausea, vomiting, diarrhea and large volume paracentesis accounted for the major bulk of patients with acute kidney dysfunction in HCV infected patients. In addition, infections ($N = 23$) and GI bleeding ($N = 9$) (the majority of which occurred in patients with advanced liver disease) appeared to play a significant role in developing AKD. In a retrospective analysis involving 82 patients with advanced liver cirrhosis, the authors found infection and GI bleeding were important predictors of AKD along with other factors like marked hyperbilirubinemia, hyponatremia and elevated liver enzymes.⁴

Chronic HCV infection has been associated with metabolic syndrome⁵ although contradicting (or contradictory) results also exist.⁶ In the present cohort of patients, we found a 42.9% prevalence of hypertension and 20.7% prevalence of DM in patients with chronic HCV infection ([Table 1](#)). Also, components of metabolic syndrome like hypertension ($P < 0.05$) and diabetes ($P < 0.05$) were significantly more often seen in patients who had an AKD event. Up to one-third (31%) of the patients having DM had an AKD event compared to only 8.9% patients without DM. In a study in ICU setting, the authors noted that patients with diabetes are at significantly increased risk of AKD.⁷ People with diabetes may be at increased risk of developing AKD, due to increased susceptibility of the kidney to adverse effects in the presence of underlying diabetic renal disease.

In 28.6% of the AKD events, a prior renal dysfunction was noted (S. Cr ≥ 1.2). Patients developing AKD with prior renal dysfunction required a significantly longer time to recover to their baseline renal function. Also a direct linear relationship was observed with peak serum creatinine level attained and the duration of recovery of

renal dysfunction to the baseline (Figures 1 and 2). Previous research supports an association between hepatitis C virus (HCV) infection with acute glomerulonephritis and AKD,⁸ but a relationship of hepatitis C and AKD events independent of acute glomerulonephritis has not been studied. The current study does not find any direct association of HCV infection related factors such as viral load or genotype in the predisposition for AKD events. Interestingly however, patients who ever received treatment with interferon irrespective of their outcome were significantly less prone to develop an event of AKD (11 (7.6%) vs. 52 (16%), $p = 0.01$). However, this does not seem to be a protective effect of interferon treatment since there was no difference in the prevalence of renal failure in those who achieved SVR vs. those who did not achieved SVR. Clearly, however patients with advanced liver disease with decompensations were more prone to develop AKD events (19% vs 0.7%, $P < 0.0001$). Decreased renal perfusion due to aggressive use of diuretics, sepsis or use of nephrotoxic antibiotics, GI bleed leading to hypotension, as well as hepato-renal syndrome are some of the mechanisms leading to AKD in these patients. Although AKD is a well-recognized complication of cirrhosis and liver failure,⁹ the majority of the cases AKD [48(76%)] occurred in patients without a decompensated/or advanced liver disease. HCV genotype 1 was the most prevalent genotype in patients with AKD, and its prevalence was not significantly different in those who did not have an event of AKD. No genotype specific prevalence of renal failure was observed. Although HCV viral load just prior to an AKD event were not available in all patients, baseline viral load clearly had no impact on the frequency of the AKD event.

HCV is increasingly an important cause of morbidity and mortality in HIV infected patients.^{10,11} 14.3% of the HIV co-infected patients developed AKD events compared to 7.7% of the patients who never had an AKD event ($P = 0.08$). In a study involving 754 patients with HIV infection, the authors noted HCV co-infected patients were significantly more prone to develop AKD events (37% vs. 21%, $P = 0.004$).¹² Also a history of intravenous drug abuse was significantly associated with AKD events (44.4% vs. 29.4%, $P = 0.02$). A study, which looked at the deleterious effect of the illicit drug abuse, noted that a significant, positive, and independent association between illicit drug use and risk for mild kidney function decline.¹³ It is possible that this mild chronic decline in renal function may have made them more prone to develop events of AKD.

In summary, we have characterized events of AKD using the RIFLE criteria in a large cohort of HCV infected patients. Clearly in HCV infected patients the single most important viral-related factor that predisposes for AKD

events is advanced liver disease and progression to decompensation. AKD events in HCV infected patients without advanced liver disease are primarily due to its unique association with high prevalence of IVDU and components of metabolic syndrome such as diabetes mellitus and hypertension. Severity of renal failure and its potential for recovery is largely dependent on the baseline serum creatinine level and independent of the viral load at baseline.

CONFLICTS OF INTEREST

All authors have none to declare.

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