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Dialysis Reduces Portal Pressure in Patients With Chronic Hepatitis C

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Abstract

The purpose of this study was to characterize changes in hepatic venous pressures in patients with chronic hepatitis C. The histology and laboratory data from patients with chronic hepatitis C who underwent a transjugular liver biopsy (TJLB) and hepatic venous pressure gradient measurement were analyzed. Portal hypertension was defined as hepatic venous pressure gradient ≥ 6 mm Hg. A single pathologist masked to hepatic venous pressure gradient scored liver sections for inflammation and fibrosis. The patients with high-grade inflammation (relative risk [RR] 2.82, $P = 0.027$, multivariate analysis) and late-stage fibrosis (RR 2.81, $P = 0.022$) were more likely to have a hepatic venous pressure gradient ≥ 6 mm Hg, while the patients on dialysis (RR 0.32, $P = 0.01$) were less likely to have a hepatic venous pressure gradient ≥ 6 mm Hg. The patients on dialysis ($n = 58$) had an elevated serum blood urea nitrogen and creatinine when compared with those who were not ($n = 75$) (47.6 ± 3.3 and 7.98 ± 0.4 vs. 25.9 ± 2.0 and 1.66 ± 0.22 mg/dL, respectively; $P < 0.001$). While the hepatic venous pressure gradient increased with the rising levels of liver fibrosis in the latter group ($P < 0.01$), it did not change in the patients on dialysis ($P = 0.41$). The median hepatic venous pressure gradient was especially low in late-stage fibrosis patients on dialysis when compared with the latter group (5 vs. 10 mm Hg, $P = 0.017$). In patients on dialysis, serum transaminases were low across all levels of fibrosis. Twenty-three of the 92 patients with early fibrosis had a hepatic venous pressure gradient ≥ 6 mm Hg. In patients with chronic hepatitis C, concomitant TJLB and hepatic venous pressure gradient measurement identify those who have early fibrosis and portal hypertension. Long-term hemodialysis may reduce portal pressure in these patients.

Keywords

Dialysis; Hepatitis C; Hepatic venous pressure gradient; Portal hypertension; Renal failure

Portal hypertension (PH) is one of the most significant sequela of cirrhosis. It contributes to all the major causes of morbidity including variceal hemorrhage, ascites, and renal

dysfunction (1,2). These complications adversely affect the quality of life and survival. Taken all together, PH is a major cause of hospital admissions that translate into significant health-care costs (3). PH is assessed by measuring the hepatic venous pressure gradient (HVPG), which is the difference between wedged (WHVP) and free hepatic vein pressure (FHVP) (4-6). Though WHVP correlates well with portal pressure, subtraction of FHVP from WHVP to determine the HVPG abrogates the impact of intra-abdominal pressure on portal pressure assessment (7-9).

In the USA and Europe, chronic hepatitis C is the most common cause of chronic liver disease. Chronic hepatitis C is also the etiology of advanced liver disease in the majority of patients undergoing liver transplantation. Newer studies have recognized the role of HVPG in predicting disease progression as well as the impact of antiviral treatment in patients with chronic hepatitis C (10-12). Blasco et al. demonstrated that HVPG ≥ 6 mm Hg may identify patients at risk for early progression of recurrent hepatitis C and help assess the long-term prognosis of patients with liver transplantation (10). Additionally, treatment with PEG-interferon and ribavirin has been shown to reduce HVPG in chronic hepatitis C patients with late-stage fibrosis and PH (13). However, changes in portal pressure during the course of early chronic hepatitis C are not known.

A recent systematic review has shown that a reduction of HVPG by $\geq 20\%$ significantly reduces the risk of variceal bleeding and mortality in patients with cirrhosis (14). Considering the measurement of HVPG requires hepatic vein catheterization, it is not routinely employed to determine the response to pharmacological treatment. Though pharmacological agents such as nonselective β -blockers reduce portal pressure and the risk of variceal hemorrhage, they are effective in less than 40% of patients with PH and cirrhosis (15-17). Renal replacement systems such as albumin dialysis have also been shown to reduce portal pressure (18). A small study (11 subjects) by Sen et al. reported that albumin dialysis reduced the HVPG $>20\%$ in the majority of patients with acute alcoholic hepatitis. Despite significant advances, the mechanisms of PH have remained poorly understood, and therapeutic options have remained limited (19,20).

We have an established protocol at our institution to measure and record the HVPG in all patients undergoing a TJLB. These available data have provided us the opportunity to perform a retrospective analysis to determine the changes in portal pressure across the increasing levels of liver fibrosis and inflammation and the impact of dialysis on HVPG in a large cohort of patients with chronic hepatitis C.

PATIENTS AND METHODS

Patients

The study was approved by the institutional review board. The hepatic venous pressures, i.e., WHVP and FHVP, were measured in all the patients undergoing TJLBs at our institution. All patients with chronic hepatitis C who underwent a TJLB and hepatic venous pressure measurement between January 2003 and May 2006 were included in this analysis. Medical charts were reviewed, and data were collected retrospectively. Criterion of renal replacement therapy requiring long-term dialysis (at least two to three times/week), distinguished the patients with and without chronic renal failure for further subgroup analysis. The mean arterial pressure (MAP) was calculated using the systolic and diastolic blood pressure measured during TJLB. The presence of pedal edema and ascites were recorded by reviewing the physical examination results and most recent abdominal imaging (ultrasound, computed tomography scan, or magnetic resonance imaging).

Hepatic venous pressure gradient measurements and TJLBs

All procedures were performed at a single institute. The right hepatic vein was catheterized via transjugular approach. The pressures were recorded in the free and wedged positions using a 4–5 Fr endhole, 0.035–0.038 lumen straight catheter, which was zeroed to the level of the right atrium. The HVPG was calculated by subtracting FHVP from WHVP. TJLBs were performed immediately after the hepatic venous pressure measurement. A 19-G core biopsy needle (Cook Medical, Bloomington, IN, USA) was used to make three to five passes. All the liver cores were more than $1.0 \times 0.1 \text{ cm}^2$ in size. The patients were monitored for 4 h after the procedure. In the renal failure patients, a TJLB was performed on their dialysis-free days.

Histological assessment

Liver histology was assessed by a single pathologist (C.D.) masked to the hepatic venous pressure measurements. The biopsy specimens were fixed in formalin, paraffin-embedded and stained with hematoxylin, eosin, and Masson trichrome, and examined under a microscope to stage fibrosis and grade inflammation using the Batts and Ludwig criteria (21). In these criteria, stage 0 is no fibrosis, stage 1 is portal fibrosis, stage 2 is periportal fibrosis, stage 3 is septal fibrosis, and stage 4 is cirrhosis. The inflammation scores graded from 0 to 4, where grade 0 is portal inflammation only, grade 1 is a mild portal inflammation with scant piecemeal necrosis and no lobular necrosis, grade 2 is a mild portal inflammation with mild piecemeal necrosis and scant lobular spotty necrosis, grade 3 is a moderate portal inflammation piecemeal necrosis and lobular spotty necrosis, and grade 4 is a marked portal inflammation with brisk piecemeal necrosis and bridging necrosis (Fig. 1A,B). The total length of the fragmented biopsies was estimated by adding the dimensions of the individual liver core fragments.

Statistical analysis

For quantitative variables, the differences between groups were analyzed using a nonparametric test such as the Kruskal–Wallis or Mann–Whitney *U*-test (SigmaStat). The Kruskal–Wallis one-way analysis of variance (ANOVA) by ranks is a nonparametric method for testing the equality of population medians among groups (<http://faculty.vassar.edu/lowry/ch14a.html>). It is identical to a one-way ANOVA with the data replaced by their ranks. It is an extension of the Mann–Whitney *U*-test to three or more groups. For normally distributed data, the difference between groups was analyzed using parametric tests such as a *t*-test. Univariate and multivariate logistic regression analyses were performed to determine the independent predictors of PH in patients with chronic hepatitis C (SAS). A *P* value of less than 0.05 was considered significant.

RESULTS

The study design is shown in Fig. 2. Between January 2003 and May 2006, 277 patients underwent hepatic venous pressures measurement and TJLB. One hundred and forty-seven patients were excluded due to non-hepatitis C etiology ($n = 140$) and inadequate hepatic venous pressure reporting ($n = 4$). The remaining 133 patients were included in the final analysis. The diagnosis of chronic hepatitis C was established by a serum serologic test and/or polymerase chain reaction.

Liver fibrosis, inflammation and venous pressures

An ANOVA was performed using the Kruskal–Wallis test to compare hepatic venous pressure measurements across the levels of liver fibrosis and inflammation. As shown in Fig. 3A and B, the WHVP and HVPG increased with progressive increase in liver fibrosis ($P <$

0.01 for both). An additional analysis revealed a significant positive association between fibrosis and WHVP and the HVPG ($r = 0.38$ and $r = 0.44$, respectively, $P < 0.0001$ for both; r is Spearman correlation coefficient).

Similar associations were observed between the inflammatory activity scores and the hepatic venous pressure. As shown in Fig. 4A and B, the WHVP and HVPG increased with a progressive increase in liver inflammation ($P = 0.03$ and $P = 0.0002$, respectively). The Spearman correlation coefficients were 0.20 ($P = 0.017$) and 0.297 ($P = 0.0005$), respectively.

Effect of dialysis on HVPG

A univariate analysis performed to assess the effect of age, race, gender, HIV co-infection, liver transplantation, and dialysis on HVPG revealed that the patients of Caucasian race (RR 1.86, 95% confidence interval [CI] 1.19–2.89, $P = 0.004$), high-grade (3,4) inflammation (RR 2.14, 95% CI 1.46–3.14, $P = 0.0003$), and late-stage (3,4) fibrosis (RR 2.33, 95% CI 1.5–3.45, $P < 0.0001$) were more likely, and the patients on dialysis were less likely to have an HVPG ≥ 6 mm Hg (RR 0.56, 95% CI 0.41–0.75, $P < 0.0001$). A logistic regression analysis for these factors indicated that high-grade inflammation (RR 2.82, 95% CI 1.12–7.08, $P = 0.027$) and late-stage fibrosis (RR 2.81, 95% CI 1.16–6.84, $P = 0.022$) were significantly associated with HVPG ≥ 6 mm Hg, while the patients on dialysis were less likely to have an HVPG ≥ 6 mm Hg (RR 0.32, 95% CI 0.14–0.77, $P = 0.010$). Therefore, to specifically evaluate the impact of dialysis on HVPG, the data were analyzed among the patients with (dialysis, $n = 58$) and without renal failure (no dialysis). The available laboratory data are summarized in Table 1. Compared with the rest of the cohort, the patients on dialysis had a significantly higher serum BUN (25.9 ± 2.0 vs. 47.6 ± 3.3 mg/dL, $P < 0.0001$) and creatinine (1.66 ± 0.22 vs. 7.98 ± 0.43 mg/dL, $P < 0.0001$). As shown in Figs. 5A and 6A, the HVPG increased progressively with an increase in fibrosis ($P < 0.01$) and inflammation ($P = 0.01$) in the patients without renal failure. There was no significant change in the HVPG with progressive increase in fibrosis ($P = 0.4$) and inflammation ($P = 0.09$) (Figs. 5B and 6B) in the patients on dialysis. To assess the effect of dialysis on fibrosis and inflammation-associated changes in the HVPG, specific comparisons were made among the patients with low- and high-grade inflammation as well as early- and late-stage fibrosis. As shown in Fig. 7A, among the patients with late-stage fibrosis, the HVPG was significantly low ($P = 0.017$) in those on dialysis compared with the rest of the cohort. Among the patients with early-stage fibrosis, a dialysis had no significant effect on the HVPG ($P = 0.22$). A similar trend was observed for patients with high-grade inflammation (Fig. 7B). However, it was not statistically significant.

A regression model using chronic kidney disease stages (I–V) did not show any effect of a worsening renal function on the risk of PH (P values for all CKD stages were not significant). While the calculated glomerular filtration rate (GFR) was significantly low in the patients on dialysis (12.46 ± 1.5 vs. 70.10 ± 4.12 , $P < 0.001$), a linear regression model showed no increased risk of PH with an increasing GFR (OR 1.01, 95% CI 0.99–1.02, $P = 0.07$). These findings suggest that the patients on dialysis were less likely to have an elevated HVPG when compared with the rest of the cohort. This effect is most pronounced in the patients with late-stage fibrosis. Similar trends were observed in serum transaminases levels among the patients on dialysis. Serum transaminases (AST and ALT) levels (Table 1) were lower in the patients on dialysis across all levels of fibrosis when compared with those who were not.

The MAP was not different among the two groups (dialysis vs. no dialysis, 97 vs. 99, $P = 0.93$). The odds of peripheral edema in the patients on dialysis were similar to the no dialysis

group (OR 0.79, 95% CI 0.42–1.45). However, the patients on dialysis had a trend toward a reduced risk of ascites (OR 0.44, 95% CI 0.18–1.09, $P = 0.064$).

PH in early fibrosis

Twenty-three (25%) of the 92 patients with early fibrosis were found to have an HVPG ≥ 6 mm Hg. Because protocol at our institution requires the patients with hepatitis C to be abstinent from alcohol for at least 3 months, the liver biopsy sections from these patients were reexamined to assess for the histological evidence of alcohol use. Seventeen patients (18%) had no histological findings suggestive of alcohol abuse. The liver biopsies from the remaining six patients had features suspicious of recent alcohol use. A microscopic examination revealed steatosis with zone 3 sclerosis in one patient, steatosis in two patients, zone 3 pericellular fibrosis in one patient, focal steatosis in one patient, and moderate steatosis with Mallory bodies in one patient. These data indicate that portal pressures can be elevated during the early course of disease in patients with chronic hepatitis C infection.

DISCUSSION

Reports in medical literature suggest that renal replacement systems such as albumin dialysis or molecular absorbent recirculating system (MARS) are effective in reducing portal pressure in patients with acute hepatitis and acute on-chronic liver failure (22). Though these studies had a small number of patients, they provide evidence that these systems have a therapeutic role in reducing portal pressures in patients with PH. This retrospective analysis from a large cohort provides evidence that a similar system may also be effective in reducing portal pressures in patients with chronic liver disease. The most relevant findings of this retrospective analysis are that in patients with chronic hepatitis C, (i) portal pressure increased with the progression of liver fibrosis and inflammation, (ii) dialysis may decrease the HVPG, and (iii) a TJB and concomitant measurement of hepatic venous pressures measurement identified those with PH who had early fibrosis. Specifically, this study suggests that renal replacement therapies are associated with a reduced risk of PH in patients with chronic liver disease.

Eighteen percent of the patients in this cohort with stage 0 to 2 fibrosis had an HVPG ≥ 6 mm Hg. In addition, the HVPG (and WHVP) increased progressively with an increase in fibrosis (Fig. 3). These data suggest that portal pressure begins to rise even before the cirrhosis is established. Bosch et al. reported that among liver transplant patients with recurrent hepatitis C, an HVPG ≥ 6 mm Hg identified those likely to decompensate (10). While the study by Bosch et al. included only liver transplant patients with recurrent hepatitis C, it raised the importance of measuring the HVPG at the time of liver biopsy in patients with chronic hepatitis C. While the current study provides the evidence that patients with early fibrosis may have elevated portal pressures, long-term studies will be needed to determine whether HVPG can predict the prognosis in non-liver transplant patients with early-stage chronic hepatitis C.

Interferon-based therapy has been shown to decrease liver inflammation in patients with chronic hepatitis C (23). A recent report suggested that the anti-hepatitis C virus (HCV) therapy reduces an HVPG that is especially pronounced in sustained responders (13). As reported by other investigators, we observed that a rising HVPG correlated strongly with the increasing stages of fibrosis (11). We also observed a positive, albeit weak relationship between HVPG and inflammatory activity scores. Our findings and these reports suggest that inflammatory activity may play a role in modulating PH in patients with chronic hepatitis C.

Inflammatory cytokines such as IL-6, IL-8, IL-10, tumor necrosis factor-alpha (TNF- α), and soluble TNF- α receptor 1 can be cleared by renal replacement systems (24). Additionally, albumin dialysis and MARS have been shown to reduce portal pressures in acute alcoholic hepatitis and acute on-chronic liver failure (18,22). These studies only compared HVPG during and after single-dialysis treatments. Hence, the long-term impact of repeated dialysis on portal pressures in patients with chronic liver disease has not been investigated before. In the current analyses, we observed that the rise in HVPG associated with an increase in fibrosis and inflammatory activity was significantly blunted in patients on dialysis. The impact of dialysis was most obvious in those with late-stage fibrosis. Additionally, as shown in Table 1, AST and ALT levels, the serum markers of chronic liver injury, were lower in patients on dialysis across all stages of fibrosis. It is possible that dialysis plays a role in modulating PH by reducing hepatic inflammation. However, the inflammatory activity scores across the levels of fibrosis were not different among the patients on and without dialysis (data not shown). The serum levels of inflammatory cytokines and their expression in hepatic tissue could have shed light on the impact of inflammation on the HVPG. However, prospective studies will be needed to determine their role on portal pressure.

Renal replacement therapies not only reduce portal pressure but also improve the hyperdynamic circulation by reducing cardiac output and increasing systemic vascular resistance in patients with acute liver failure (25). The improvement in hemodynamics may further help in lowering portal pressure by reducing the splanchnic inflow. This effect is thought to be due to the removal of albumin-bound toxins as well as nitric oxide. Whether hemodialysis, when used over extended periods of time, has similar effects is not known. Due to the retrospective nature of this study, these parameters were not measured in the present analysis. An additional factor that has not been addressed by this analysis is the impact of prior anti-HCV therapy on the HVPG in the patients studied. As indicated earlier, prior interferon treatment may reduce the HVPG and can impact the results of this study. In this cohort, only a minor proportion had received an interferon-based therapy (data not shown). Among the patients with normal renal function, seven had received anti-HCV treatment for less than 6 months, and two patients received it for 48 weeks. A history of treatment could not be determined in the six patients. In contrast, the patients on dialysis were treatment-naïve. Based on these data, we argue that the suboptimal treatment received by a minority of the patients is unlikely to confound the results of this analysis.

At our institution, hepatic venous pressures are measured by using a straight catheter. Balloon-tipped, as well as straight, catheters have been used to measure hepatic venous pressures. Balloon-tipped catheters are thought to measure WHVP over a wider hepatic vascular territory that allows repeated measurements from the same hepatic vein without moving the catheter, and avoid the decompressive effects of proximal venous-to-venous shunts (4). A previous study and a recent review have demonstrated that there is a good correlation among the measurement made by using straight and balloontipped catheters (7,26). Occlusion technique is well standardized at our institution and interventional radiologists follow a standard protocol for the measurement of hepatic venous pressures.

CONCLUSION

As indicated in the discussion earlier, this analysis has raised numerous questions that will require prospective studies to answer. Nevertheless, observations made from the large cohort suggests that in patients with chronic hepatitis C, (i) portal pressure rises before the establishment of cirrhosis, (ii) HVPG measured at the time of a TJLB may help assess the severity of chronic hepatitis, and (iii) hemodialysis has a significant impact on portal pressure.

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FIG. 1.

Representative photomicrographs of fibrosis stages and grades of inflammation are shown. (A) Photomicrographs of trichromestained liver section with increasing stages of fibrosis (1-4) are shown. Fibrous bands are stained blue (white arrows). Expansion of fibrous septae indicates late-stage fibrosis. (B) Photomicrographs of hematoxylin and eosin-stained liver section with increasing grades of inflammation (1-4) are shown. Infiltration of hepatic parenchyma with mononuclear inflammatory cells (white arrows) indicates high-grade inflammation (see Patients and Methods section for details).

FIG. 2.
Study design.

FIG. 3. Effect of fibrosis on hepatic venous pressures in patients with chronic hepatitis C. Stage of fibrosis is shown on the x-axis. WHVP (A) and HVP (B) are shown on the y-axis. Box plots show the median HVP, 25th to 75th percentile box, and complete range of measurements. There was significant association between stage of fibrosis and hepatic venous pressures. WHVP and the HVP increased with the progression of fibrosis (Kruskal–Wallis test, $P < 0.01$ for both; n indicates the number of patients in each group).

FIG. 4.

Effect of inflammation on hepatic venous pressures in patients with chronic hepatitis C. Grade of inflammation is shown on the x-axis. WHVP (A) and HVP (B) are shown on the y-axis. Box plots show the median WHVP and HVP, 25th to 75th percentile box, and complete range of measurements. Because the number of patients with an inflammation grade of 0 ($n = 2$) and 4 ($n = 1$) were too low to calculate the median inflammatory scores, they were grouped with the patients with inflammation grades 1 and 3, respectively. The WHVP and HVP increased with severity of inflammation (Kruskal–Wallis test, $P = 0.03$ and $P = 0.0002$, respectively; n indicates the number of patients in each group).

FIG. 5.

Effect of dialysis on HVPg across stages of fibrosis in patients with chronic hepatitis C. Stage of fibrosis is shown on the x-axis and HVPg is shown on the y-axis. Box plots show median HVPg, 25th to 75th percentile box, and complete range of measurements. (A) With progressive increase in fibrosis, the HVPg increased in the patients with normal renal function (solid bars, Kruskal-Wallis test, $P < 0.01$). (B) In the patients on dialysis, there was no difference in the HVPg across all levels of fibrosis (hatched bars, Kruskal-Wallis test, $P = 0.4$; n indicates the number of patients in each group).

FIG. 6.

Effect of dialysis on HVPg across grades of inflammation in patients with chronic hepatitis C. Grade of inflammation is shown on the x-axis and HVPg is shown on the y-axis. Box plots show the median HVPg, 25th to 75th percentile box, and complete range of measurements. Because the number of patients with an inflammation grade of 0 ($n = 2$) and 4 ($n = 1$) were too low to calculate the median inflammatory scores, they were grouped with the patients with inflammation grades of 1 and 3, respectively. (A) With a progressive increase in inflammation, the HVPg increased in patients with normal renal function (solid bars, Kruskal-Wallis test, $P = 0.01$; n indicates the number of patients in each group). (B) No such change was observed in patients on dialysis (hatched bars, Kruskal-Wallis test, $P = 0.09$; n indicates the number of patients in each group).

FIG. 7. Impact of dialysis on HVPg among patients with early- and late-stage fibrosis as well as low- and high-grade inflammation. Stages of fibrosis (A) and grade of inflammation (B) are shown on the x-axis and HVPg is shown on the y-axis. Box plots show the median HVPg, 25th to 75th percentile box, and complete range of measurements. As shown in panel A, there is no difference in the HVPg among the patients with stage 0–2 fibrosis. However, the patients on dialysis (hatched bars) with stage 3–4 fibrosis have a significantly lower HVPg when compared with rest of the cohort (solid bars). As shown in panel B, a similar trend was observed in patients with high-grade inflammation. However, it was not statistically significant (*n* indicates the number of patients in each group).

TABLE 1
Laboratory characteristics

	Dialysis (<i>n</i> = 58)	No dialysis (<i>n</i> = 75)	<i>P</i> value *
BUN (mg/dL)			
Stage 0	43.5	28.5	0.193
Stage 1	48.0	27.0	0.00176
Stage 2	39.0	18.5	0.0011
Stage 3	56.5	19.0	0.041
Stage 4	17.0	16.0	0.213
Creatinine (mg/dL)			
Stage 0	9.05	1.05	0.03
Stage 1	8.15	1.25	<0.00001
Stage 2	7.95	1.35	<0.00001
Stage 3	4.80	1.10	0.02
Stage 4	4.10	0.90	0.0073
T. Protein (g/dL)			
Stage 0	7.6	5.20	0.111
Stage 1	7.9	6.445	0.0073
Stage 2	8.5	7.45	0.156
Stage 3	7.1	7.20	0.87
Stage 4	6.4	7.40	0.27
Albumin (g/dL)			
Stage 0	4.1	3.15	0.312
Stage 1	3.9	3.3	0.0401
Stage 2	3.9	3.7	0.4189
Stage 3	3.55	3.4	0.627
Stage 4	2.2	2.9	0.1654
Alkaline phosphatase (U/L)			
Stage 0	109.0	233.5	0.665
Stage 1	108.0	149.0	0.093
Stage 2	112.0	124.5	0.5383
Stage 3	92.0	172.0	0.0895
Stage 4	163.0	132.0	0.138
AST (U/L)			
Stage 0	26.5	52.0	0.3123
Stage 1	31.0	44.0	0.01793
Stage 2	38.0	90.5	0.01414
Stage 3	47.0	101.5	0.249
Stage 4	28.0	82.0	0.00979
ALT (U/L)			
Stage 0	36.5	65.0	0.3123
Stage 1	35.0	63.0	0.0054

	Dialysis (n = 58)	No dialysis (n = 75)	P value *
Stage 2	45.5	91.0	0.02434
Stage 3	45.0	88.5	0.43
Stage 4	33.0	65.0	0.0128
Total bilirubin (mg/dL)			
Stage 0	0.5	0.60	0.665
Stage 1	0.6	0.75	0.142
Stage 2	0.6	0.90	0.0794
Stage 3	0.8	1.25	0.363
Stage 4	1.7	1.20	0.534
Platelet count (×1000/mcL)			
Stage 0	225.5	180.0	0.665
Stage 1	214.0	141.5	0.005
Stage 2	193.0	125.5	0.00609
Stage 3	93.5	136.0	0.363
Stage 4	52.0	75.0	0.5659
PT (seconds)			
Stage 0	11.75	11.90	0.8852
Stage 1	11.70	12.00	0.3656
Stage 2	12.30	13.40	0.2549
Stage 3	12.65	13.35	0.5048
Stage 4	17.40	13.95	0.3397

The values in the table are reported as medians.

PT, prothrombin time.

* Mann–Whitney *U*-test.