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Diagnostic Discordance for Hepatitis C Virus Infection in Hemodialysis: Correlations with Clinical and Laboratory Features

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CORRESPONDENCE

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DIAGNOSTIC DISCORDANCE FOR HEPATITIS C VIRUS INFECTION IN HEMODIALYSIS: CORRELATIONS WITH CLINICAL AND LABORATORY FEATURES

To the Editor:

Similarly to Kalantar-Zadeh et al,[1] we evaluated hepatitis C virus (HCV) status in hemodialysis patients by means of enzyme immunoassay (antibody to HCV EIA) and qualitative HCV RNA assay based on transcription-mediated amplification (TMA).[2] The prevalence of HCV infection (TMA positive [TMA^+]) was greater than that in the study by Kalantar-Zadeh et al[1] (31.7% versus 15%). Sensitivity of EIA (TMA as gold standard) was low (63% versus 53%) in both studies (Table 1). However, the following aspects need specific consideration.

HCV EIAs, invariably based on antigens from genotype 1, are suboptimal for screening populations with predominant non-1b genotype.[3] HCV genotyping (Versant HCV Lipa; Bayer Corp, Tarrytown, NY) in our TMA^+ cases showed that genotype 3a was prevailing (72 of 116 cases; 62%).[2] However, non-1b genotypes were distributed equally in TMA^+/EIA-negative (EIA^-) and TMA^+/EIA^+ patients (27 of 38 [71%] versus 44 of 69 patients [64%]; $P = 0.6$). Hence, a false-negative EIA result cannot be attributed to genotype-dependent factors.[2]

EIA^- results in TMA^+ patients may indicate an early stage of HCV infection. In support of this notion is our finding, in contrast to that of Kalantar-Zadeh et al,[1] of shorter hemodialysis duration in TMA^+/EIA^- compared with TMA^+/EIA^+ patients. Against it are the lower aminotransferase levels of TMA^+/EIA^- compared with TMA^+/EIA^+ patients in both studies (Table 1). Furthermore, the high sensitivity and specificity of newly elevated aminotransferase levels for the diagnosis of acute hepatitis C in hemodialysis patients[4] makes this hypothesis highly unlikely.

Finally, there was no difference in overall mortality between TMA^+/EIA^+ and TMA^+/EIA^- patients (Table 1). Because malnutrition-inflammation-cachexia syndrome is associated with poor outcome in hemodialysis patients,[5] this finding contradicts the hypothesis that malnutrition-inflammation-cachexia syndrome is responsible for the low sensitivity of EIA.

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Table 1. Prevalence of Antibodies to HCV Assessed by Means of a Third-Generation EIA

	Both Tests$^+$ (TMA^+/EIA^+)	TMA^+ Only (TMA^+/EIA^-)	EIA^+ Only (TMA^-/EIA^+)	No HCV Infection (TMA^-/EIA^-)	*P**
No. of patients	72	44	16	234	
Age (y)	61.4 ± 11.6	60.5 ± 13.1	60.2 ± 15	60.6 ± 14.8	0.916
Female sex	27 (37.5)	16 (36.4)	6 (37.5)	72 (30.8)	0.494
Duration of hemodialysis (mo)	88.1 ± 58.3	36.1 ± 33.6	75.2 ± 47.5	36.2 ± 37.4	0.0001
Diabetes mellitus	6 (8.3)	8 (18.2)	1 (6.3)	46 (19.7)	0.082
Aspartate aminotransferase (U/L)	31 ± 14	18 ± 8	27 ± 11	20 ± 21	0.001
Alanine aminotransferase (U/L)	38 ± 22	20 ± 12	32 ± 20	22 ± 19	0.0001
Mortality†	33 (45.8)	15 (34.1)	5 (31.3)	95 (40.6)	0.538

NOTE. Values expressed as number (percent) or mean ± SD unless noted otherwise. Values are for all patients with end-stage renal disease on maintenance hemodialysis therapy (n = 366) in the renal units (n =5) of the region Thessaly in central Greece. Clinical and laboratory features and outcome (4-year overall mortality) are according to the presence of antibodies to HCV or HCV RNA in serum (antibody to HCV EIA; HCV3.0, Ortho, Raritan, NJ) and HCV RNA assessed by means of TMA assay (TMA; Bayer Corp, Tarrytown, NY).

*Analysis of variance or Pearson chi-square, when appropriate. The EIA^+ only group includes only 16 patients and was not included in analyses.

†Represents 4-year overall mortality.

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In Reply:

We appreciate the comments by Stefanidis et al. Their findings of the low sensitivity of hepatitis C virus (HCV) enzyme immunoassay (EIA) for the detection of HCV infection in patients on maintenance hemodialysis therapy are similar to ours[1] and highlight the limitations of such testing in these subjects. Unlike our findings, they report that HCV EIA-negative (EIA^-)/transcription-mediated amplification (TMA)-positive (TMA^+) test results, compared with EIA^+/TMA^+, were more likely to occur in patients with shorter hemodialysis therapy duration. These findings are of interest and in contrast to what has been described in patients with other serious chronic conditions in which HCV EIA false negativity in those with chronic infection tends to occur more frequently in advanced stages of the underlying disease. For example, human immunodeficiency virus–infected individuals with chronic HCV infection are more likely to be EIA^- with advanced immunosuppression.[2]

We also should note that the lack of difference in mortality between EIA^+/TMA^+ patients and other groups seen by Stefanidis et al might be caused by the cross-sectional design (ie, survival bias and/or type II error [lack of statistical power]). Furthermore, observations of lower transaminase levels in EIA^-/TMA^+ patients compared with those with EIA^+/TMA^+ results, as reported by both Stefanidis et al and us,[1] also are not straightforward. Design limitations of the investigations by us and Stefanidis et al underscore the need for longitudinal studies to better understand the significance of HCV infection in persons on maintenance hemodialysis therapy, including those with discordant diagnostic test results. The observed association between greater mortality and HCV infection in persons on maintenance hemodialysis therapy[3,4] further suggests that interventions to treat HCV in this population may have merit and be worthy of further investigation.

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ARE HOMOCYSTEINE AND MTHFR GENOTYPE POLYMORPHISM ASSOCIATED WITH ARTERIOVENOUS FISTULA PATENCY?

To the Editor:

In a recent article, Mallamaci et al[1] concluded that native arteriovenous fistula thrombosis in hemodialysis patients is associated with hyperhomocysteinemia. We appreciated this prospective cohort study controlling for access type; however, the methylenetetrahydrofolate reductase (MTHFR) genotype polymorphism failed to predict fistula outcome despite its correlation with serum homocysteine level. Although the investigators listed data for possible risk factors in all study subjects, differences in risk factors other than plasma homocysteine levels (such as prevalence of diabetes or supplemented dose of folic acid) were not shown among the 3 tertile groups. A recent meta-analysis by Den Heijer et al[2] reported that homocysteine levels are associated with risk for venous thrombosis, as is the *MTHFR* 677TT genotype; however, the 677TT genotype had no effect on venous thrombosis in patients in North America, probably resulting from the greater intake of folate and riboflavin there. Use of folate and other relevant vitamin supplements might decrease events of access thrombosis in patients harboring the