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Liver Digest

A weekly update of PLRC happenings

December 5, 2019

PITTSBURGH LIVER RESEARCH CENTER
A partnership of University of Pittsburgh & UPMC

www.livercenter.pitt.edu

Featured Faculty - Dr. Eric Lagasse

In this issue

PLRC Mini-Retreat February 3

PLRC Mini-Retreat

Mon, 2/03/2020

10:30 am - 3:30 pm

S100A BST

- **10:30-11:30** - First group of Pilot and Feasibility awardees from the 2019-2020 cycle will each give a 10-minute presentation on their research
- **11:30-12:00** - Lunch (provided)
- **12:00-1:00** - Second group of Pilot and Feasibility awardees from the 2019-2020 cycle will each give a 10-minute presentation on their research
- **1:30-3:00** - Grant-writing presentation - Dr. Gavin Arteel and Dr. Nick Giannoukakis
- **3:00-3:30** - Q and A
- **3:30-4:00** - Closing remarks - Dr. Paul Monga

The full schedule of Enrichment activities is posted on **https://www.livercenter.pitt.edu/events**.

Clinical Component Update

The webpage for the Clinical Component has been updated to reflect its newly revised format and mission. The Clinical Component offers services in:

- Commercialization
- Diagnostics
- Biostatistical support
- Consultation -- both clinical and basic research

A request form is available on the webpage.

Please take a look! **https://www.livercenter.pitt.edu/clinical-component**

Faculty Highlights

PLRC members collaborating on manuscripts are noted in red.

Original Article:

Zhu X, Chao K, Li M, **Xie W**, Zheng H, Zhang JX, Hu PJ, Huang M, Gao X, Wang XD. Nucleoside diphosphate-linked moiety X-type motif 15 R139C genotypes impact 6-thioguanine nucleotide cut-off levels to predict thiopurine-induced leukopenia in Crohn's disease patients. World J Gastroenterol. 2019 Oct 14;25(38):5850-5861. doi: 10.3748/wjg.v25.i38.5850. PubMed PMID: 31636477; PubMed Central PMCID: PMC6801191.

ABSTRACT

BACKGROUND: Thiopurine-induced leukopenia (TIL) is a life-threatening toxicity and occurs with a high frequency in the Asian population. Although nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) variants significantly improve the predictive sensitivity of TIL, more than 50% of cases of this toxicity cannot be predicted by this mutation. The potential use of the 6-

thioguanine nucleotide (6TGN) level to predict TIL has been explored, but no decisive conclusion has been reached. Can we increase the predictive sensitivity based on 6TGN by subgrouping patients according to their NUDT15 R139C genotypes?

AIM: To determine the 6TGN cut-off levels after dividing patients into subgroups according to their NUDT15 R139C genotypes.

METHODS: Patients' clinical and epidemiological characteristics were collected from medical records from July 2014 to February 2017. NUDT15 R139C, thiopurine S-methyltransferase, and 6TGN concentrations were measured.

RESULTS: A total of 411 Crohn's disease patients were included. TIL was observed in 72 individuals with a median 6TGN level of 323.4 pmol/8 × 108 red blood cells (RBC), which was not different from that of patients without TIL (P = 0.071). Then, we compared the 6TGN levels based on NUDT15 R139C. For CC (n = 342) and CT (n = 65) genotypes, the median 6TGN level in patients with TIL was significantly higher than that in patients without (474.8 vs 306.0 pmol/8 × 108 RBC, P = 9.4 × 10-5; 291.7 vs 217.6 pmol/8 × 108 RBC, P = 0.039, respectively). The four TT carriers developed TIL, with a median 6TGN concentration of 135.8 pmol/8 × 108 RBC. The 6TGN cut-off levels were 411.5 and 319.2 pmol/8 × 108 RBC for the CC and CT groups, respectively.

CONCLUSION: The predictive sensitivity of TIL based on 6TGN is dramatically increased after subgrouping according to NUDT15 R139C genotypes. Applying 6TGN cut-off levels to adjust thiopurine therapies based on NUDT15 is strongly recommended.

For full text, please **click here.**

Original Article:

Rogal S, Youk A, Zhang H, Gellad WF, Fine MJ, Good CB, Chartier M, DiMartini A, Morgan T, **Bataller R**, Kraemer KL. Impact of Alcohol Use Disorder Treatment on Clinical Outcomes among Patients with Cirrhosis. Hepatology. 2019 Nov 23. doi: 10.1002/hep.31042. PubMed PMID: 31758811.

ABSTRACT

Despite significant medical and economic consequences of coexisting alcohol use disorder (AUD) in patients with cirrhosis, little is known about AUD treatment patterns and their impact on clinical outcomes in this population. We aimed to characterize the use of and outcomes associated with AUD treatment in patients with cirrhosis. This retrospective cohort study included Veterans with cirrhosis who received Veterans Health Administration (VA) care and had an index diagnosis of AUD between 2011 and 2015. We assessed the baseline factors associated with AUD treatment (pharmacotherapy or behavioral therapy) and clinical outcomes for 180 days following the first AUD diagnosis code within the study time frame. Among 93,612 Veterans with cirrhosis, we identified 35,682 with AUD, after excluding 2,671 who had prior diagnoses of AUD and recent treatment. Over 180 days following the index diagnosis of AUD, 5,088 (14%) received AUD treatment, including 4,461 (12%) who received behavioral therapy alone, 159 (0.4%) who received pharmacotherapy alone, and 468 (1%) who received both behavioral and pharmacotherapy. In adjusted analyses, behavioral and/or pharmacotherapy-based AUD treatment was associated with a significant reduction in incident hepatic decompensation (6.5% vs. 11.6%, adjusted odds ratio [AOR]=0.63, 95% confidence interval [CI]=0.52-0.76) and a non-significant decrease in short-term all-cause mortality (2.6% vs. 3.9%, AOR=0.79, 95% CI=0.57-1.08), and a significant decrease in long-term all-cause mortality (51% vs. 58%, AOR=0.87, 95% CI=0.80, 0.96). CONCLUSION: Most patients with

cirrhosis and coexisting AUD did not receive behavioral or pharmacotherapy treatment for AUD over a 6-month follow-up. The reductions in hepatic decompensation and mortality suggest that future studies should focus on delivering evidence-based AUD treatments to patients with coexisting AUD and cirrhosis.

For full text, please **click here**.

Original Article:

Furlan A, Tublin ME, Yu L, Chopra KB, Lippello A, **Behari J**. Comparison of 2D Shear Wave Elastography, Transient Elastography, and MR Elastography for the Diagnosis of Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. AJR Am J Roentgenol. 2019 Nov 12:1-7. doi: 10.2214/AJR.19.21267. PubMed PMID: 31714842.

ABSTRACT

OBJECTIVE. The aim of the present study was to compare the diagnostic accuracy of liver stiffness measurements (LSMs) obtained using MR elastography (MRE), transient elastography (TE), and 2D shear wave elastography (SWE) in patients with biopsy-proven nonalcoholic fatty liver disease (NAFLD). SUBJECTS AND METHODS. We prospectively enrolled 62 adult subjects (mean age [± SD], 50 ± 13 years; 58% women; body mass index [weight in kilograms divided by the square of height in meters], 35 ± 7). Two-dimensional SWE, MRE, and TE were performed at a mean of 105 ± 86 days after liver biopsy. The area under the ROC curve (AUROC) values and 95% CIs for the corresponding LSMs (expressed in kilopascals) were calculated, with significant fibrosis (Metavir liver fibrosis score, F2-F4) and advanced fibrosis (F3-F4) used as outcome measures. Pairwise comparisons of AUROC values were conducted using the DeLong test. Statistical significance was set at $p < 0.05$. RESULTS. For the 62 subjects, valid LSMs were obtained for 57 subjects with the use of 2D SWE, for 59 subjects with TE, for 59 subjects with MRE, and for

54 subjects with all three modalities combined. The AUROC values (95% CIs) of 2D SWE, TE, and MRE for the diagnosis of significant fibrosis were 0.80 (0.67-0.92), 0.77 (0.64-0.89), and 0.85 (0.74-0.95), respectively. The AUROC values (95% CIs) of 2D SWE, TE, and MRE for the diagnosis of advanced fibrosis were 0.89 (0.80-0.98), 0.86 (0.77-0.95), and 0.95 (0.89-1.00), respectively. Pairwise comparisons revealed similar diagnostic accuracy for significant fibrosis (2D SWE vs MRE, p = 0.431; 2D SWE vs TE, p = 0.317; and MRE vs TE, p = 0.052) and advanced fibrosis (2D SWE vs MRE, p = 0.348; 2D SWE vs TE, p = 0.293; and MRE vs TE, p = 0.059). CONCLUSION. For patients with biopsy-proven NAFLD, 2D SWE, MRE and TE exhibited comparable and very good to excellent diagnostic accuracy for advanced fibrosis and comparable but lower accuracy for significant fibrosis.

For full text, please **click here**.

Original Article:

Wahlang B, Hardesty JE, Head KZ, Jin J, Falkner KC, Prough RA, Cave MC, **Beier JI**. Hepatic injury caused by the environmental toxicant vinyl chloride is sex-dependent in mice. Toxicol Sci. 2019 Nov 27. pii: kfz236. doi: 10.1093/toxsci/kfz236. PubMed PMID: 31774537.

ABSTRACT

Vinyl chloride (VC), a common industrial chemical, has been associated with hemangiosarcoma and toxicant-associated steatohepatitis (TASH) in men working at rubber-production plants. Our group previously demonstrated that chronic VC inhalation at environmentally-relevant levels (<1ppm) in male mice exacerbated hepatic injury caused by high fat diet (HFD) feeding. Because VC studies on TASH have only been performed in male models, the objective of this study is to examine VC inhalation in female mice in the context of TASH mechanisms. Male and female C57Bl/6 mice

were fed either a low-fat diet (LFD) or HFD and exposed to VC or room air using an inhalation chamber, for 12 weeks (6 hours, 5 days/week); and plasma and liver samples were collected after euthanasia. Compared to males, females were less susceptible to HFD+VC-induced obesogenic effects demonstrated by lower body weight and fat composition. Histological analysis revealed that while VC exacerbated HFD-induced steatosis in males, this effect was absent in females. Additionally, females were more resistant to VC-induced hepatic inflammation while males had increased liver weights and higher hepatic Tnfα mRNA levels. Systemic markers of hepatic injury, namely alanine aminotransaminase and thrombin/antithrombin levels were increased by HFD+VC co-exposures only in males. Additionally, females did not show significant cell death as previously reported in males. Taken together, the results suggested that VC inhalation led to sex-dependent liver and metabolic toxicity. This study implicated the importance of assessing sex differences in environmental basic science and epidemiologic studies to better identify at-risk populations in both men and women.

For full text, please **click here**.

Funding Opportunities

Gilead Sciences Research Scholars Cardiovascular Comorbidities Program

Gilead Sciences, Inc. / Gilead Sciences Pty Ltd

Bradley-Alavi Student Fellowships

Society of Nuclear Medicine and Molecular Imaging (SNMMI)

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