Paper alert

A selection of interesting papers that were published in the month before our press date in major journals likely to report important results in gastroenterology and hepatology.

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Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease

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Background & Aims: Multiparametric magnetic resonance (MR) imaging has been demonstrated to quantify hepatic fibrosis, iron, and steatosis. The aim of this study was to determine if MR can be used to predict negative clinical outcomes in liver disease patients.

Methods: Patients with chronic liver disease (n = 112) were recruited for MR imaging and data on the development of liver related clinical events were collected by medical records review. The median follow-up was 27 months. MR data were analysed blinded for the Liver Inflammation and Fibrosis score (LIF; < 1, 1–1.99, 2–2.99, and ≥ 3 representing normal, mild, moderate, and severe liver disease, respectively), T2* for liver iron content and proportion of liver fat. Baseline liver biopsy was performed in 102 patients.

Results: Liver disease aetiologies included non-alcoholic fatty liver disease (35%) and chronic viral hepatitis (30%). Histologically, fibrosis was mild in 54 (48%), moderate in 17 (15%), and severe in 31 (28%) patients. Overall mortality was 5%. Ten patients (11%) developed at least one liver related clinical event. The negative predictive value of LIF < 2 was 100%. Two patients with LIF 2–2.99 and eight with LIF ≥ 3 had a clinical event. Patients with LIF ≥ 3 had a higher cumulative risk for developing clinical events, compared to those with LIF < 1 (P = 0.02) and LIF 1–1.99 (P = 0.03). Cox regression analysis including all 3 variables (fat, iron, LIF) resulted in an enhanced LIF predictive value.

Conclusions: Non-invasive standardised multiparametric MR technology may be used to predict clinical outcomes in patients with chronic liver disease.

J Hepatol 2016; 64:308–315. doi: 10.1016/j.jhep.2015.10.009.

Aging of liver transplant registrants and recipients: trends and impact on waitlist outcomes, post-transplantation outcomes, and transplant-related survival benefit

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Background & Aims: Epidemiologic factors have generated increased demand for liver transplantation among older patients. We aimed to describe trends in age among liver transplant registrants and recipients and the effect of age on waitlist and post-transplantation outcomes and on transplant-related survival benefit.

Methods: We obtained data from the United Network for Organ Sharing on adults who were listed for liver transplantation (N = 122,606) or underwent liver transplantation (N = 60,820) from 2002 to 2014 in the United States. Competing risks analysis was used to model waitlist outcomes and Cox proportional hazards analysis to model post-transplantation survival. These models were also used to estimate 5-year transplant-related survival benefit for different age groups, calculated as the difference between waitlist and post-transplantation life expectancy.

Results: Between 2002 and 2014, the mean age of liver transplant registrants increased from 51.2 to 55.7 years, with a more prominent increase in hepatitis C virus–positive (50.9–57.9 years) than hepatitis C virus–negative (51.3–54.3 years) registrants. The proportion of registrants aged ≥ 60 years increased from 19% to 41%. In hepatitis C virus–negative patients, aging trends were driven by increasing proportions of patients with hepatocellular carcinoma or nonalcoholic steatohepatitis. Among transplant recipients, increasing age was associated with increasing mortality before transplantation and decreasing likelihood of transplantation. Among transplant recipients, increasing age was associated with increasing post-transplantation mortality. There was little difference in 5-year transplant-related survival benefit between different age groups who had the same Model for End-Stage Liver Disease score.

Conclusion: Dramatic aging of liver transplant registrants and recipients occurred from 2002 to 2014, driven by aging of the hepatitis C virus–positive cohort and
increased prevalence of nonalcoholic steatohepatitis and hepatocellular carcinoma. Increasing age does not affect transplant-related survival benefit substantially because age diminishes both post-transplantation survival and waitlist survival approximately equally.

Gastroenterology 2016; 150:441–453.e6. doi: 10.1053/j.gastro.2015.10.043

Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy + β-blocker for prevention of variceal rebleeding

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Gastroesophageal variceal bleeding in patients with cirrhosis is associated with significant morbidity and mortality, as well as a high rebleeding risk. Limited data are available on the role of transjugular intrahepatic portosystemic shunt (TIPS) with covered stents in patients receiving standard endoscopic, vasoactive, and antibiotic treatment. In this multicenter randomized trial, long-term endoscopic variceal ligation (EVL) or glue injection + β-blocker treatment was compared with TIPS placement in 72 patients with a first or second episode of gastric and/or esophageal variceal bleeding, after hemodynamic stabilization upon endoscopic, vasoactive, and antibiotic treatment. Randomization was stratified according to Child-Pugh score. Kaplan-Meier (event-free) survival estimates were used for the endpoints rebleeding, death, treatment failure, and hepatic encephalopathy. During a median follow-up of 23 months, 10 (29%) of 35 patients in the EVL group died, compared to 0 of 37 (0%) patients in the TIPS group, developed variceal rebleeding (P = 0.001). Mortality (TIPS 32% vs. endoscopic 26%; P = 0.418) and treatment failure (TIPS 38% vs. endoscopic 34%; P = 0.685) did not differ between groups. Early hepatic encephalopathy (within 1 year) was significantly more frequent in the TIPS group (35% vs. 14%; P = 0.035), but during long-term follow-up this difference diminished (38% vs. 23%; P = 0.121).

Conclusion: In unselected patients with cirrhosis, who underwent successful endoscopic hemostasis for variceal bleeding, covered TIPS was superior to EVL + β-blocker for prevention of variceal rebleeding, but did not improve survival. TIPS was associated with higher rates of early hepatic encephalopathy.

Hepatology 2016; 63:581–589. doi: 10.1002/hep.28318

Magnetic resonance elastography is superior to acoustic radiation force impulse for the diagnosis of fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease: A prospective study

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Magnetic resonance elastography (MRE), an advanced magnetic resonance–based imaging technique, and acoustic radiation force impulse (ARFI), an ultrasound-based imaging technique, are accurate for diagnosing nonalcoholic fatty liver disease (NAFLD) fibrosis. However, no head-to-head comparisons between MRE and ARFI for diagnosing NAFLD fibrosis have been performed. We compared MRE versus ARFI head-to-head for diagnosing fibrosis in well-characterized patients with biopsy-proven NAFLD. This cross-sectional analysis of a prospective cohort involved 125 patients (54.4% female) who underwent MRE, ARFI, and contemporaneous liver biopsies scored using the Nonalcoholic Steatohepatitis Clinical Research Network histological scoring system. The performances of MRE versus ARFI for diagnosing fibrosis were evaluated using area under the receiver operating characteristic curves (AUROCs). The mean (± standard deviation) age and body mass index were 48.9 (± 15.4) years and 31.8 (± 7.0) kg/m2, respectively. For diagnosing any fibrosis (≥ stage 1), the MRE AUROC was 0.799 (95% confidence interval [CI] 0.723–0.875), significantly higher than the ARFI AUROC of 0.664 (95% CI 0.568–0.760). In stratified analysis by presence or absence of obesity, MRE was superior to ARFI for diagnosing any fibrosis in obese patients (P < 0.001) but not in nonobese patients (P = 0.722). The MRE AUROCs for diagnosing ≥ stages 2, 3, and 4 fibrosis were 0.885 (95% CI 0.816–0.953), 0.934 (95% CI 0.863–1.000), and 0.882 (95% CI 0.729–1.000); and the ARFI AUROCs were 0.848 (95% CI 0.776–0.921), 0.896 (95% CI 0.824–0.968), and 0.862 (95% CI 0.721–1.000). MRE had higher AUROCs than ARFI for discriminating dichotomized fibrosis stages at all dichotomization cutoff points, but the AUROC differences decreased as the cutoff points (fibrosis stages) increased.

Conclusion: MRE is more accurate than ARFI for diagnosing any fibrosis in NAFLD patients, especially those who are obese.

Hepatology 2016; 63:453–461. doi: 10.1002/hep.28337

Ramosetron reduces symptoms of irritable bowel syndrome with diarrhea and improves quality of life in women

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Background & Aims: Previous studies have indicated that serotonin-3-receptor antagonists might have a sex-specific effect in patients with irritable bowel syndrome with diarrhea (IBS-D). Alosetron has been approved for the treatment of only women, and ramosetron has been approved for the treatment for only men. We performed a randomized, placebo-controlled, phase 3 study to determine whether ramosetron reduces symptoms of IBS-D in women.
Methods: We performed a prospective study of 576 female outpatients with IBS-D (according to the Rome III criteria), from February 2013 through February 2014, at 70 academic Gastroenterology Departments in Japan. After a 1-week baseline period, subjects received either 2.5 µg ramosetron (n=292) or placebo (n=284) once daily for 12 weeks. Primary end points were the monthly rates of response for relief from overall IBS symptoms and increased stool consistency at the last evaluation point. Quality of life (QOL) also was quantified.

Results: A significantly higher proportion of patients given ramosetron reported global improvement (50.7%; 95% confidence interval [CI], 44.8–56.6) than patients given placebo (32.0%; 95% CI, 26.7–37.8)—a difference of 18.6% (95% CI, 10.7–26.3; P<0.001). The relative risk was 1.58 (95% CI, 1.29–1.94) and the number needed to treat was 6 (95% CI, 4–10). A significantly higher proportion of patients in the ramosetron group reported increased stool consistency (40.8%; 95% CI, 35.1–46.6%) than in the placebo group (24.3%; 95% CI, 19.4–29.7%)—a difference of 16.5% (95% CI, 8.9%–24.0%; P<0.001). Patients receiving ramosetron had significant reductions in abdominal pain and discomfort (P=0.001) and greater improvement in QOL (P=0.002) compared with placebo. Ramosetron induced constipation in 11.0% of patients.

Conclusion: In a randomized, placebo-controlled study of 576 women with IBS-D, 2.5 µg ramosetron per day reduced symptoms and increased stool consistency and QOL. ClinicalTrials.gov no: NCT01870895.

Gastroenterology 2016; 150:358–366.e8. doi: 10.1053/j.gastro.2015.10.047

A randomized, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis

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Objective: To investigate the efficacy and safety of two different budesonide formulations (effervescent tablet for orodispersible use (BET) and viscous suspension (BVS)) with different daily dosages for short-term treatment of eosinophilic oesophagitis (EOE).

Design: Adults with active EoE (n=76) randomly received 14 days' treatment with either BET 2×1 mg/day (BET1, n=19) or BET 2×2 mg/day (BET2, n=19), or BVS 2×5 ml (0.4 mg/ml)/day (BVS, n=19) or placebo (n=19) in a double-blind, double-dummy fashion, with a 2-week follow-up. Primary end point was histological remission (mean of <16 eosinophils/mm2 hpf). Secondary end points included endoscopy score, dysphagia score, drug safety and patient's preference for drug formulation.

Results: Histological remission occurred in 100%, 94.7% and 94.7% of budesonide (BET1, BET2, BVS, respectively) and in 0% of placebo recipients (P<0.0001). The improvement in total endoscopic intensity score was significantly higher in the three budesonide groups compared with placebo. Dysphagia improved in all groups at the end of treatment; however, improvement of dysphagia persisted only in those treated with BET1 (P=0.0196 vs. placebo). There were no serious adverse events. Local fungal infection (stained fungi) occurred in two patients of each budesonide group (10.5%). The effervescent tablet was preferred by 80% of patients.

Conclusion: BET or BVS was highly effective and safe for short-term treatment of EoE. The 1 mg (twice daily) dosage was equally effective as the 2 mg twice daily dosage. The majority of patients preferred the effervescent tablet formulation.

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Investigation of faecal volatile organic metabolites as novel diagnostic biomarkers in inflammatory bowel disease

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Background: The aetiology of inflammatory bowel disease (IBD) remains poorly understood. Recent evidence suggests an important role of gut microbial dysbiosis in IBD, and this may be associated with changes in faecal volatile organic metabolites (VOMs).

Aim: To describe the changes in the faecal VOMs of patients with IBD and establish their diagnostic potential as non-invasive biomarkers.

Methods: Faecal samples were obtained from 117 people with Crohn’s disease (CD), 100 with ulcerative colitis (UC), and 109 healthy controls. Faecal VOMs were extracted using solid-phase micro-extraction and analysed by gas chromatography mass spectrometry. Data analysis was carried out using partial least squares-discriminate analysis (PLS-DA) to determine class membership based on distinct metabolic profiles.

Results: The PLS-DA model showed clear separation of active CD from inactive disease and healthy controls (P<0.001). Heptanal, 1-octen-3-ol, 2-piperidinone and 6-methyl-2-heptanone were up-regulated in the active CD group [variable important in projection (VIP) score 2.8, 2.7, 2.6 and 2.4, respectively], while methanethiol, 3-methyl-phenol, short-chain fatty acids and ester derivatives were found to be less abundant (VIP score of 3.5, 2.6, 1.5 and 1.2, respectively). The PLS-DA model also separated patients with small bowel CD from healthy controls and those with colonic CD from UC (P<0.001). In contrast, less distinct separation was observed between active UC, inactive UC and healthy controls.

Conclusions: Analysis of faecal volatile organic metabolites can provide an understanding of gut metabolic
changes in IBD. It has the potential to provide a non-invasive means of diagnosing IBD, and can differentiate between UC and CD.

Aliment Pharmacol Ther 2016; 43:596–611. doi: 10.1111/apt.13522

Outcomes of esophageal dilation in eosinophilic esophagitis: Safety, efficacy, and persistence of the fibrostenotic phenotype

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Objectives: Esophageal dilation is commonly performed in eosinophilic esophagitis (EoE), but there are few long-term data. The aims of this study were to assess the safety and long-term efficacy of esophageal dilation in a large cohort of EoE cases, and to determine the frequency and predictors of requiring multiple dilations.

Methods: We conducted a retrospective cohort study in the University of North Carolina EoE Clinicopathological Database from 2002 to 2014. Included subjects met consensus diagnostic criteria for EoE. Clinical, endoscopic, and histologic features were extracted, as were dilation characteristics (dilator type, change in esophageal caliber, and total number of dilations) and complications. Patients with EoE who had undergone dilation were compared with those who did not and also stratified by whether they required single or multiple dilations.

Results: Of 509 EoE patients, 164 were dilated a total of 486 times. Those who underwent dilation had a longer duration of symptoms before diagnosis (11.1 vs. 5.4 years, \(P < 0.001\)). Ninety-five patients (58%) required >1 dilation (417 dilations total, mean of 4.4 ± 4.3 per patient). The only predictor of requiring multiple dilations was a smaller baseline esophageal diameter. Dilation was tolerated well, with no major bleeds, perforations, or deaths. The overall complication rate was 5%, primarily due to post-procedural pain. Of 164 individuals dilated, a majority (58% or 95/164) required a second dilation. Of these individuals, 75% required repeat dilation within 1 year.

Conclusions: Dilation in EoE is well-tolerated, with a very low risk of serious complications. Patients with long-standing symptoms before diagnosis are likely to require dilation. More than half of those dilated will require multiple dilations, often needing a second procedure within 1 year. These findings can be used to counsel patients with fibrostenotic complications of EoE.

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