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Non-Invasive Detection of Liver Disease in Community Health Centers Enhances Patient Engagement, Improves Outcomes

Robert G. Gish, MD, Medical Director, Hepatitis B Foundation

In 2013, Dr. Gish joined the consulting faculty at La Maestra in San Diego, California, to establish a liver care program in the Federally Qualified Health Care clinic. His integral role in the diagnosis, treatment and management of patients with NAFLD and NASH provides valuable guidance for this specialized sector of patient care.

Among the diseases that impact Americans and their caregivers, non-alcoholic fatty liver disease (NAFLD), also referred to as metabolic associated fatty liver disease (MAFLD), is gaining more attention. An umbrella term for a range of liver conditions affecting people who drink little to no alcohol, NAFLD affects approximately 100 million individuals in the United States. The prevalence for its more serious form, non-alcoholic steatohepatitis (NASH), is expected to increase by 63% by 2030.

In some cases, NASH may lead to cirrhosis, liver cancer, liver transplant and death. NASH, which is associated with nonspecific symptoms, and is often underdiagnosed and underreported, recently became the most common reason for a liver transplant in women and older patients.

Most patients with NASH experience few specific symptoms, especially in the early stages of the disease. When a patient feels well or has vague symptoms, it can be challenging for physicians and caregivers to convince the patient that they may have a dangerous condition.

Community health centers, which deliver exceptional care to medically underserved

populations, share a common goal of providing coordinated, culturally competent and community-directed primary and preventive health care services. Today they deliver care to 29 million people across the country.

Physicians at community health centers play a critical role in not only helping to educate patients about the importance of liver for overall health, but also identifying the best approaches for preventing the progression of NAFLD.

Who is at Risk?

People most at risk for developing NAFLD or NASH have obesity, type 2 diabetes (T2D), hyperlipidemia and/or metabolic syndrome. Hispanic and Latino populations are disproportionately affected by NAFLD, depending on genetic factors, access to health care or the prevalence of chronic diseases, such as metabolic syndrome or diabetes.

Health center patients have higher rates of chronic conditions than the general population. This is important to note because the presence of T2D accelerates the progression of liver disease in patients with NAFLD, and NAFLD is an independent predictor

associated with a more than two-fold increase in developing T2D.

Researchers have found NAFLD, hepatitis C, liver cancer and liver transplants are prevalent in 40-80% of people who have T2D and in 30-90% of people who are obese. Being overweight or obese is responsible for about 85% of fatty liver disease.

Enhancing Patient Engagement

Because NAFLD and NASH are so tightly intertwined with obesity, diabetes and lifestyle, a “whole person” approach to patient engagement is needed to support behavioral changes that will result in better outcomes across the co-morbid conditions affecting the individual patient.

Early detection is needed because lifestyle modifications and strict control of metabolic risk factors are the most effective treatment. Because disease progression is typically slow, patients can be managed well by primary care physicians. NAFLD patients with advanced liver fibrosis should be referred to specialist care for further assessment.

While finding and managing fibrotic NASH is an important component to addressing liver disease, patients with steatosis alone are at a greater risk of cardiovascular mortality and morbidity.

Physicians should consider integrating non-invasive, point-of-care liver examinations as a way to improve patient intake, outcomes, lower costs and enhance income stream. FibroScan, for example, is an FDA cleared technology for the diagnosis and monitoring

of adult patients as part of an overall evaluation of liver health.

Unlike blood tests that measure circulating markers of inflammation, such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), this tool directly and non-invasively measures physical properties of stiffness and liver fat.

It provides reproducible results, allowing for both diagnosis and monitoring of liver stiffness and liver fat, and has been recognized as a cost-effective tool for screening and also identifying cirrhosis in people with NAFLD. This information can support care management across key components of the metabolic syndrome – diabetes and hyperlipidemia.

Early Interventions

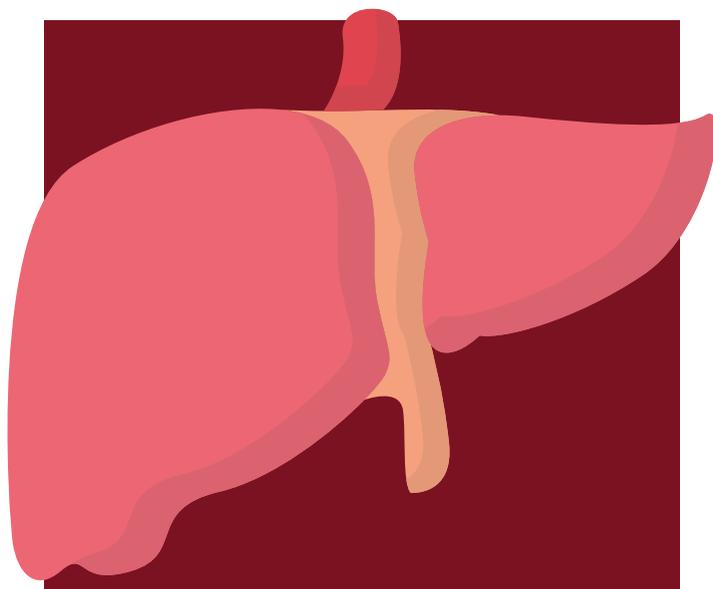
When it comes to treating NAFLD, diet and exercise interventions are the first line of therapy, with the goal of decreasing body weight and modifying cardio-metabolic risk factors related to metabolic syndrome. In the early stages of NAFLD, a healthy diet and weight loss of at least 7% might be sufficient. Patients are often treated with vitamin E as well. Aggressive management of hypertension, diabetes and lipid disorder is also key.

San Diego-based La Maestra, a health center serving low-income and immigrant residents, has seen an alarming rise in liver disease. Because of this, every liver patient at La Maestra undergoes a rapid, non-invasive point of care examination, which validates that they have determined elastography with CAP to be an essential part of a patient’s workup, along with a full abdominal ultrasound that includes special liver cancer biomarkers, a liver panel that includes liver enzymes and liver function, chemistry panel and a CBC as well as APRI, FIB4 NAFLD score calculations.

La Maestra has found it to be particularly useful to share the patient’s liver health score and CAP with patients who have NAFLD to illustrate the change in liver fat and the need for adjusting their treatment and calculation of the FAST score.

Physician practices working in the community health center setting can play a significant role in helping to reverse the nation’s liver disease epidemic through early detection and monitoring of NAFLD/NASH.

Ultimately, having a non-invasive tool at the point of care to examine liver health provides quantifiable information that can improve individual health outcomes, lower payer costs by avoiding expensive, invasive interventions and enhance the financial performance of a physician practice. ■



Early Life Cow's Milk Linked to Increased Asthma Risk

Kenny Walter

There could be a connection between food allergies and the development of asthma or recurrent wheeze, especially for cow's milk, according to new research.

A team, led by Hiroshi Tachimoto, MD, PhD, Division of Molecular Epidemiology, Jikei University School of Medicine, evaluated whether asthma or recurrent wheeze among children were changed by avoiding supplementing breastfeeding with cow's milk formula (CMF) in the first 3 days of life.

In the randomized, unmasked, clinical trial, the investigators examined 312 newborns at a single university hospital in Japan. The study began in October 2013, with follow-up examinations occurring until January 2020.

The 312 infants in the study all had a risk for atopy.

“The findings of this study suggest that avoiding CMF supplementation in the first 3 days of life has the potential to reduce the risk of asthma or recurrent wheeze in young children, especially among those with high vitamin D or high IgE levels,” the authors wrote.

Each newborn was randomized (1:1) and assigned to either a breastfeeding group with or without amino acid-based elemental formula for at least the first 3 days of life or a breastfeeding group with at least 5 mL/d of cow's milk formula from the first day of life for 5 months. Follow-up examinations for participants showing signs of atopy were conducted at 24 months.

The investigators sought main outcomes of asthma or recurrent wheeze diagnosed by the pediatric allergy specialists from the trial. The researchers also stratified subgroups by serum levels of 25-hydroxyvitamins D and IgE.

A total of 77 (51%) of the infants in the no cow's milk formula and 81 (53.6%) in the cow's milk group underwent extended follow-up due to atopic conditions.

Asthma or recurrent wheeze was found in 15 (9.9%) of the children in the no cow's milk formula group, which was significantly less than the children in the cow's milk formula group ($n = 27$ [17.9%]; risk difference, -0.079 ; 95% CI, -0.157 to -0.002).

For patients with vitamin D levels above the median at 5 months, asthma or recurrent wheeze developed in 5 (6.4%) participants in the no cow's milk formula group, which was substantially less than in the children in the cow's milk formula group ($n = 17$ [24.6%]; risk difference, -0.182 ; 95% CI, -0.298 to -0.067 ; P for interaction = 0.04).

In the highest quartile group of total IgE at 24 months, asthma or recurrent wheeze developed in only 2 children (5.3%) in the no cow's milk formula group, significantly less than the children in the cow's milk formula group ($n = 14$; 43.8%; risk difference, -0.385 ; 95% CI, -0.571 to -0.199 ; P for interaction = 0.004).

“The findings of this study suggest that avoiding CMF supplementation in the first 3 days of life has the potential to reduce the risk of asthma or recurrent wheeze in young children, especially among those with high vitamin D or high IgE levels,” the authors wrote.

The study, “Effect of Avoiding Cow's Milk Formula at Birth on Prevention of Asthma or Recurrent Wheeze Among Young Children,” was published online in *JAMA Network Open*. ■



Prenatal Acetaminophen Exposure Associated with Increased ADHD Risk

Jonathan Alicea

A new study found an association between prenatal acetaminophen exposure and an increased risk for ADHD. These results have led the investigators to suggest that the drug's use during pregnancy should be re-evaluated.

Despite acetaminophen's widespread use, they noted increasing concerns that it may impair fetal brain development. This may be done directly by inducing oxidative stress and apoptosis in the brain as well as indirectly through disrupting essential developmental hormones.

In this prospective birth cohort study, Brennan Baker, MA, and colleagues at Columbia University Medical Center and Mailman School of Public Health, assessed meconium samples for acetaminophen in newborns as well as further evaluated the same population for ADHD at ages 6-7.



They assessed resting-state brain connectivity using magnetic resonance imaging. Attention problems and hyperactivity were assessed using the Behavioral Assessment System for Children Parent Report Score.

The investigators used linear and logistic regressions to estimate the associations between meconium acetaminophen levels and outcomes. And finally, they used causal mediation analysis to test if resting-state brain mediates the association between prenatal exposure and hyperactivity.

Enrollment occurred from September 2007-September 2009, and data was collected from September 2007-January 2020.

Overall, they included 345 children in their analysis.

Of the population, 51.3% were boys and the mean age at follow-up was 6.58 years.

Maker and team noted that acetaminophen was detected in 199 meconium samples (57.7%), with ADHD being detected in 33 children (9.6%).

Acetaminophen detection in meconium was associated with about a 2.5-fold increased odds of ADHD when compared with non-detection (OR, 2.43; 95% CI, 1.41-4.21).

The investigators further stratified acetaminophen meconium into 3 levels of prevalence. Thus, high levels of the drug were associated with a 4-fold increased odds of ADHD (OR, 4.10; 95% CI, 2.41-6.9)—versus a lower odds in low levels of detected acetaminophen (OR, 1.44; 95% CI, 0.79-2.63).

Further, a linear modeling of meconium acetaminophen revealed that each doubling of exposure increased the odds of ADHD by 10% (OR, 1.10; 95% CI, 1.02-1.19).

It was also reported that children with greater levels of acetaminophen detected in meconium showed increased negative connectivity between the frontoparietal and default mode network nodes and 6 clusters in the sensorimotor cortices. The investigators noted this mediated an indirect effect on increased child hyperactivity (14% increase; 95% CI, 1%-26%).

Previous studies have linked use of the pain management medication during pregnancy with increased risk for ADHD, but only one other study has directly measured acetaminophen levels.

They also addressed previous limitations of using and relying on maternal recall of drug use assessed through questionnaires and other such methods.

“By using a direct measurement of prenatal acetaminophen exposure that is unbiased by maternal recall, these results add evidence in support of the association between prenatal acetaminophen use and child ADHD,” Baker and team wrote. “Thus, the association between prenatal acetaminophen and ADHD may be even stronger than previously estimated.”

The study, Association of Prenatal Acetaminophen Exposure Measured in Meconium With Risk of Attention-Deficit/Hyperactivity Disorder Mediated by Frontoparietal Network Brain Connectivity,” was published online in *JAMA Pediatrics*. ■

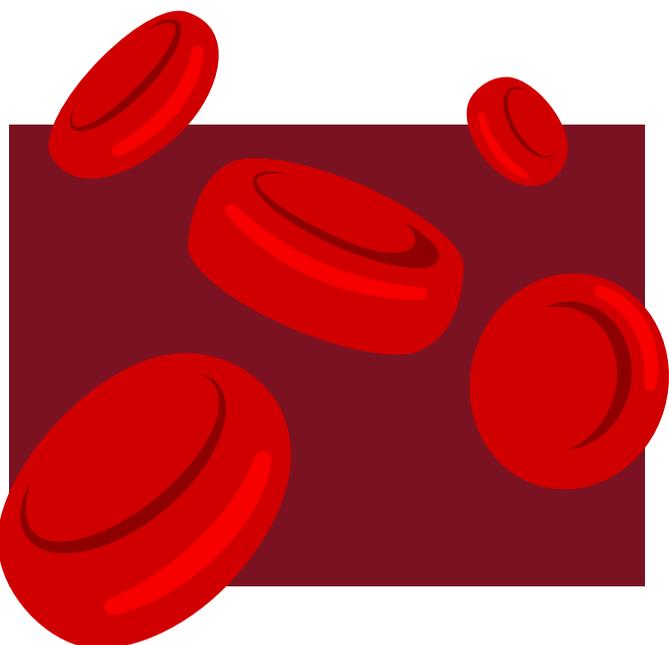
Sickle Cell Disease Linked to Vitamin D Deficiency, Low Bone Marrow Density

Jonathan Alicea

Findings from a new study showed children with sickle cell disease have increased rates of vitamin D deficiency and low bone marrow density. The investigators suggested that such patients should be screened for vitamin D levels regularly.

In this cross-sectional study, a team led by Mohamed Ahmed Badr, MD, from Zagazig University, Egypt sought to assess the relationship between vitamin D levels and bone marrow density in children with sickle cell disease.

“This study concluded that Vitamin D deficiency is a major nutritional health problem in patients with sickle cell disease,” the investigators wrote. “[It] emphasizes the need for vitamin D level screening for all SCD patients.”



Previous literature has suggested a higher risk of bone disease in the sickle cell disease population, and yet little has been known about bone marrow density in such patients and any potential association with 25(OH)D levels.

Therefore, the investigators enrolled a total of 30 patients—53.3% of whom were male—who had sickle cell disease and were regularly following up at the Pediatric Hematology outpatient clinics of Zagazig University Hospitals. The ages of the patients ranged from 6-18 years.

Of the entire population, a majority (60%) of the population had sickle cell anemia, followed by an equal distribution of sickle anemia plus B-thalassemia (20%) and the sickle cell trait (20%).

They excluded patients with known conditions affecting growth or nutritional status, chronic liver and kidney function abnormalities, who were undergoing treatment with drugs that affected the skeleton and bone density, or who had other hemoglobinopathies.

The study was conducted from February 2018 to August 2018.

Vitamin D insufficiency was defined as a 25(OH)D of 21-29 ng/mL.

Further, bone mineral density was measured using the dual-energy X-ray absorptiometry (DEXA) scan. The investigators measured bone mineral density at the posterior-anterior spine, thus adhering to the International Society for Clinical Densitometry (ISCD) recommendation for children.

The results of the DEXA scan were expressed with a Z-score, which is the number of standard deviations from the mean bone marrow density compared with other children of the same age, sex, and ethnicity. Z-scores below -2 SD were considered abnormal, and scores between -1 and -2 were considered low or osteopenia.

Thus, Badr and colleagues found that bone marrow density of lumbar vertebrae 1 – 4 was abnormal in 86.5% of all patients (mean Z-score, -2.33).

Total body bone marrow density was abnormal in 80.0% of the population (Z-score, -1.45).

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They also noted that the mean vitamin D level among the entire group was 16.22 ng/mL, with a range from 7.71 ng/mL – 33.68 ng/mL. Additionally, 83.3% of the population had a Vitamin D deficiency.

Of those with sickle cell anemia, 88.9% had a deficiency, followed by a deficiency in 100% of the sickle cell anemia plus thalassemia population ($P < .05$).

And finally, they found no significant correlation between Z-score of bone marrow density (L1-L4 and total body) and Vitamin D level among the studied sickle cell population.

“This study concluded that Vitamin D deficiency is a major nutritional health problem in patients with sickle cell disease,” the investigators wrote. “[It] emphasizes the need for vitamin D level screening for all SCD patients.”

They encouraged that treatment of vitamin D hypovitaminosis and maintenance with vitamin D doses that meet the daily requirements should be ensured for these patients.

The study, “Assessment of Vitamin D Level and Osteoporosis in Children with Sickle Cell Anemia,” was published online in *The Egyptian Journal of Hospital Medicine*. ■

The Eyes Are Windows into Sport-Related Concussion in Adolescents

Kenneth Bender

Pupillary light reflex (PLR) metrics could provide a fast, portable and objective physiologic biomarker of sport-related concussion (SRC) in adolescents, according to investigators who compared the measures in athletes with clinically diagnosed concussion and in healthy controls.

Christina Master, MD, Sports Medicine and Performance Center, Children’s Hospital of Philadelphia, and colleagues described their study as the first to demonstrate that quantitative PLR metrics can differentiate concussed adolescent athletes from healthy control participants.

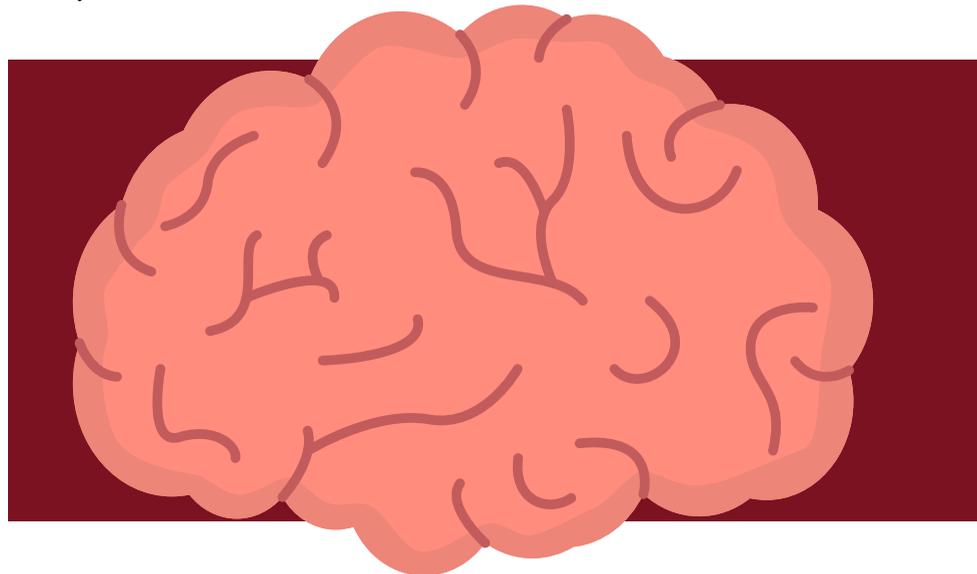
“The results presented here may be clinically relevant because these metrics are easily obtained via automated dynamic infrared pupillometry (DIP), and the measurable objective differences discriminate well between adolescents with and without concussion, indicating potential future utility in the diagnosis of concussion in the sports setting,” Master and colleagues wrote.

In accompanying commentary, Wesley Beaulieu, PhD

and Adam Glassman, MS, Jaeb Center for Health Research, described the study as not only the first to evaluate PLR metrics in adolescents with concussion but, with a larger sample size than similar studies in adults, with sufficient power for strict statistical testing of the possible diagnostic utility.

“Specifically, they used the Bonferroni procedure, a simple approach that maintains the probability of finding at least 1 false-positive result at the desired level.” Beaulieu and Glassman observed. “We were happy to see that the authors of this study used an appropriate method for controlling the false-positive rate, given that several interconnected outcomes were analyzed in their study.”

Master and colleagues measured 9 different parameters of PLR in 98 athletes with concussion diagnosis at a median 12 days after the injury, and in 134 healthy athletes participating in the study as controls before their sport season. All but 1 of the pupillary light reflex parameters, latency, had value ranges that were statistically significantly more likely to occur in concussion.



The 8 associated with the trauma were: maximum pupil diameter, minimum pupil diameter, percentage pupil constriction, peak and average constriction velocity, average dilation velocity, T75 (time for pupil redilation from minimum diameter to 75% maximum diameter) and calculated peak dilation velocity.

In addition to distinguishing concussion, the investigators determined that exercise had an effect on PLR metrics in control individuals. Specifically, they found those who exercised before pupillary assessment had smaller maximum and minimum pupil sizes with lower peak and average constriction/dilation velocities compared with the control individuals who did not exercise before the measure.

Master and colleagues also found prolongation of T75 in girls with concussion, which supports previously described sex-based differences following concussion.

“There are no previously reported sex differences in T75 in control participants, in either adults or children,” the investigators noted, “making the sex differences in T75 in girls with concussion of particular interest.”

Beaulieu and Glassman agreed with Master and colleagues that PLR metrics show promise as an objective, reproducible biomarker for SRC in adolescent athletes, but suggest that further study is required.

“The results presented here may be clinically relevant because these metrics are easily obtained via automated dynamic infrared pupillometry (DIP), and the measurable objective differences discriminate well between adolescents with and without concussion, indicating potential future utility in the diagnosis of concussion in the sports setting,”

“Future prospective studies that evaluate individuals before and after SRC onset are needed to establish the utility of PLR in diagnosing concussion,” Beaulieu and Glassman advised.

The study, “Utility of Pupillary Light Reflex Metrics as a Physiologic Biomarker for Adolescent Sport-Related Concussion,” was published online in *JAMA Ophthalmology*. ■

Outcomes of Acute Coronary Syndrome in Inflammatory Bowel Disease Patients

Rachel Lutz

While hospitalizations for acute coronary syndrome (ACS) in patients with inflammatory bowel disease (IBD) were stable in recent years, the ACS-related risk profiles and mortality were modestly favorable in patients with IBD-ACS compared to non-IBD with ACS patients, according to a new study.

A team of investigators from several countries retrospectively compared IBD patients without ACS to IBD patients with ACS in order to determine the epidemiology and outcomes of ACS in patients with IBD.

The investigators noted that IBD has been associated with an increased risk of ACS and heart failure in prior studies that focused on epidemiology. There are

differences between Crohn’s disease (CD) and ulcerative colitis (UC) as they related to ACS that the team wanted to explore as well.

There were about 6.8 million non-IBD plus ACS patients in the investigation that were compared to 24,220 IBD and ACS hospitalizations (of which about half had UC). The patients were hospitalized between 2005-2015. The investigators collected data about admissions, mortality, risk profiles, management strategies, and in-hospital mortality, which was broken down by IBD/ACS, non-IBD/ACS, and CD and UC.

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The IBD patients were more likely to be female, white, have higher income, and have a higher prevalence of connective tissue disease, pulmonary disease, coagulopathy, depression, liver disease, hypothyroidism, weight loss, anemia, and atrial fibrillation compared to the patients without IBD, the study authors found.

The mean age of the IBD cohort was 67 years, and about two-thirds were insured by Medicare/Medicaid.

The most common traditional cardiovascular risk factors included hypertension, dyslipidemia, smoking, diabetes, chronic kidney disease, and obesity. The study authors learned that patients with IBD and ACS were less likely to have these traditional cardiovascular risk factors. However, the comorbidities and complications that are frequently associated with IBD were strongly associated with mortality from ACS, the study authors said.

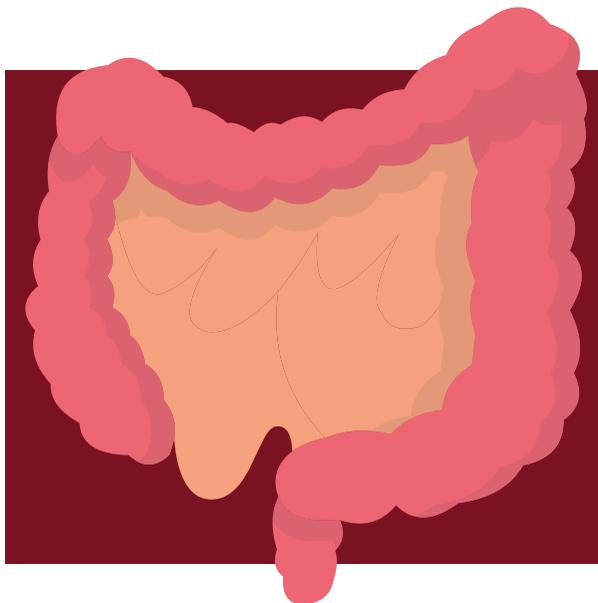
The patients with CD in the study were admitted to the hospital with ACS at an average of 3 years younger than the patients with UC, the study authors noted. On the subject of age, the study authors said that ACS in CD was found at a younger age and at a higher proportion of females compared to the general population (48% vs. 40%, respectively), but these demographics in UC patients were aligned with the general population.

The overall in-hospital mortality for patients with IBD and ACS was 5.3% and was higher in patients without IBD, the study authors said. Additionally, they found the overall mortality rate was similar between patients with UC and patients with CD (4.1% and 3.7%, respectively). They also noted their results were similar across groups regardless of age, sex, ACS type, and utilization of invasive management strategy for ACS.

Study author Gayatri Pemmasani, MBBS, told *HCPLive*[®] the team concluded the Medical comorbidities and complications that were more prevalent in patients with IBD—including gastrointestinal bleeding, weight loss, coagulopathy, and electrolyte abnormalities—were greatly associated with increased ACS mortality.

“These data regarding the predictors of mortality provide guidance for the early identification of these factors and appropriate management of patients with IBD who are at a higher risk of death from ACS,” Pemmasani said. “More aggressive medical management of IBD to reduce the inflammation, disease

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progression, and incidence of these disease-related comorbidities may help reduce cardiovascular morbidity and mortality.”

Investigators added they identified a two- to three-fold higher risk of myocardial infarction in patients with IBD compared to patients without IBD, and a slightly higher rate in patients with CD compared to those with UC.

“More aggressive medical management of IBD to reduce the inflammation, disease progression, and incidence of these disease-related comorbidities may help reduce CVD-related morbidity and mortality,” investigators concluded.

The study, “Epidemiology and Clinical Outcomes of Patients With Inflammatory Bowel Disease Presenting With Acute Coronary Syndrome,” was published online in *Inflammatory Bowel Diseases*. ■