Burning mouth syndrome needs to consider the gut-brain axis from three types of pain: nociceptive, neuropathic, and nociplastic pain

To the Editor,

The gut-brain axis (GBA) consists of bidirectional communication between the central nervous system and the intestinal tract, linking emotional centers of the brain with peripheral gut function. The GBA may be involved in the etiology of central painful diseases, but the relationship is not fully understood. I read with great interest the article on the etiology of burning mouth syndrome (BMS) by Russo et al. [1]. They showed that BMS has a multifactorial etiopathology, including laryngopharyngeal reflux, hormonal and salivary changes related to aging and menopause, and oral flora, which may induce neurodegeneration in the orofacial region [1]. I agree with the perspective that signals from the gastrointestinal tract, including the gut microbiota, influence unexplained chronic pain. However, there is little evidence regarding GBA as the etiology of BMS. Therefore, I propose to organize their perspectives in three dimensions for future research: receptor, nerve, and brain circuit (Table I).

Burning mouth syndrome is an intractable chronic pain disorder of unknown cause characterized by burning sensation without any organic abnormality in the oral mucosa. Pain complaints of BMS patients range from tingling, stickiness, and an indescribable pressure-like pain with discomfort. There are three types of pain: nociceptive pain, neuropathic pain, and nociplastic pain, and the pain of BMS patients includes all of these elements. The review by Russo et al. [1] discusses gastrointestinal disease as a cause of nociceptive pain such as an increase in transient receptor potential vanilloid1 (TRPV1) receptors and neuropathic pain such as neuroinflammation. However, the uncomfortable multifocal widespread pain of BMS patients is classified as nociplastic pain, unlike nociceptive or neuropathic pain. The mechanisms that underlie this type of pain are not entirely understood, but it is thought that augmented central nervous system pain and sensory processing and altered pain modulation play prominent roles [2]. Nociplastic pain may be accompanied by gastrointestinal symptoms as well as other symptoms of central nervous system origin, such as fatigue, sleep, memory, and mood problems,

Table I. Three types of pain and their mechanisms in burning mouth syndrome

Dimension	Type of Pain	Mechanism	Sexual Dimorphism
Receptor	Nociceptive Pain	Laryngopharyngeal reflux Increase in TRPV1 receptor Change in saliva composition Microbiota	Two hit theory by estrogen
Nerve	Neuropathic Pain	Neuroinflammation Neurovascular compression Microbiota	Lack of dopamine receptor in descending pain inhibitory pathway in female rats Decreased neuroprotection with decreased estrogen
Brain Circuit	Nociplastic Pain	Dopaminergic dysregulation Increase in salience network Microbiota	Increase in corticotropin-releasing factor (CRF)-producing neurons in female rats Decreased neuroprotection with decreased estrogen

which may implicate the GBA as the etiopathology of this pain formation. I suggest that a perspective of nociplastic pain in BMS patients be added to the review of Russo et al. [1].

Interestingly, the majority of BMS patients are perimenopausal women. Sexual dimorphism may be involved in the pathogenesis of BMS. However, since the time of onset is associated with menopause, a two-stage hit is predicted to occur, with female hormones forming a preparatory state and the onset of the disease occurring as female hormones decrease. At the receptor level, estrogen has a dual aspect on the TRPV1 receptor. Estrogen not only increases TRPV1 receptor expression, but also reduces pain by facilitating its translocation from the cell surface to the intracellular space. Therefore, two-hit theory by estrogen hypothesis has been proposed [3]. At the nerve level, estrogen plays a dual role of neuroprotection in the repair of damaged nerves and neuropathic induction. Even at the brain circuit level, estrogen is not only neuroprotective, but also increases the number of anxiety pain neurons to the basal ganglia dopaminergic neurons. Corticotropin-releasing factor (CRF)-producing neurons in the bed nucleus of the stria terminalis (BNST) that convey discomfort due to central pain exhibit a female-biased sexual dimorphism that increases with estrogen [4]. CRF-producing neurons are connected via the lateral thalamus to dopamine loop, an area whose neurotransmission may be altered by signals from the gastrointestinal tract [5].

In conclusion, BMS patients induce pain in three dimensions: nociceptive, neuropathic, and nociplastic pain, and GBA may influence the etiology of each dimension. Further research is needed to elucidate the underlying mechanisms linking pain formation and GBA.

Takahiko Nagamine
Psychiatric Internal Medicine, Sunlight Brain Research Center, Hofu, Japan

Correspondence: Takahiko Nagamine, tnagamine@outolook.com

Conflicts of interest: None.
DOI: 10.15403/jgld-5322

REFERENCES

1. Russo M, Crafa P, Guglielmetti S, Franzoni L, Fiore W, Di Mario F. Burning Mouth Syndrome Etiology: A Narrative Review. J Gastrointestin Liver Dis 2022;31:223-228. doi:10.15403/jgld-4245
2. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet 2021;397:2098-2110. doi:10.1016/S0140-6736(21)00392-5
3. Nagamine T. Two-hit theory by estrogen in burning mouth syndrome. J Dent Sci 2022;17:1833-1834. doi:10.1016/j.jds.2022.06.009
4. Uchida K, Otsuka H, Morishita M, et al. Female-biased sexual dimorphism of corticotropin-releasing factor neurons in the bed nucleus of the stria terminalis. Biol Sex Differ 2019;10:6. doi:10.1186/s13293-019-0221-2
5. Breen DP, Halliday GM, Lang AE. Gut-brain axis and the spread of α-synuclein pathology: Vagal highway or dead end? Mov Disord 2019;34:307-316. doi:10.1002/mds.27556

Reply,

To the Editor,

We would like to express our gratitude to the Nagamine T. for the insightful letter [1] regarding our recent narrative review on the etiology of burning mouth syndrome (BMS) [2]. The proposed perspectives on the involvement of the gut-brain axis (GBA) in the pathogenesis of BMS, particularly the three-dimensional framework considering receptors, nerves, and brain circuits, add valuable dimensions to the ongoing discourse on this challenging condition.

The suggestion to incorporate a perspective on nociplastic pain in BMS patients is particularly intriguing. We appreciate the emphasis on understanding the multifaceted nature of pain in BMS, encompassing nociceptive, neuropathic, and nociplastic dimensions. Acknowledging the potential role of the GBA in influencing the etiology of each of these dimensions opens up new avenues for research and therapeutic exploration. The interconnectedness of gastrointestinal symptoms and central nervous system manifestations in BMS patients indeed warrants a comprehensive investigation into the mechanisms linking pain formation and the GBA.

Furthermore, the author‘s exploration of sexual dimorphism and the two-hit theory involving estrogen in BMS pathogenesis is a valuable addition to the discussion. The insights into estrogen‘s dual aspect on TRPV1 receptors at the receptor level, its roles at the nerve level in neuroprotection and neuropathic induction, and its impact on brain circuitry, including the bed nucleus of the stria terminalis (BNST) and dopamine loop, provide a compelling framework for understanding the hormonal influence on BMS.

The proposed research dimensions, as outlined in Table 1, present a structured approach for future investigations into the complex interplay between the GBA and BMS. The comprehensive review of relevant literature and the incorporation of references contribute to the credibility and depth of the proposed perspectives.

In conclusion, we are grateful for the constructive feedback and the valuable insights provided by the author. The proposed dimensions for future research offer a solid foundation for expanding our understanding of BMS etiology, paving the way for targeted therapeutic interventions. We look forward to the continued exploration of these perspectives by the research community.

Francesco Di Mario
Department of Medicine and Surgery, University of Parma, Parma, Italy

Correspondence: Francesco Di Mario, francesco.dimario@unipr.it

Conflicts of interest: None.
DOI: 10.15403/jgld-5411

REFERENCES

1. Nagamine T. Burning mouth syndrome needs to consider the gut-brain axis from three types of pain: nociceptive, neuropathic, and nociplastic pain. J Gastrointestin Liver Dis 2023;32. doi:10.15403/jgld-5322

2. Russo M, Crafa P, Guglielmetti S, Franzoni L, Fiore W, Di Mario F. Burning Mouth Syndrome Etiology: A Narrative Review. J Gastrointestin Liver Dis 2022;3:223-228. doi:10.15403/jgld-4245

Challenges in the management of checkpoint inhibitor induced liver injury

To the Editor,

We read with great interest the paper *Digestive Toxicities Secondary to Immune Checkpoint Inhibition Therapy – Reports of Rare Events. A systematic Review* published in the *J Gastrointestin Liv Dis* in 2021 [1]. Regarding liver toxicities, the authors found case reports of rare events such as: cholestatic liver injury (sclerosing cholangitis with one fatal case, vanishing bile duct syndrome), granulomatous hepatitis, lipodystrophy, hepatic sinusoidal obstruction syndrome [1].

The following case report illustrates the multiple diagnostic and treatment challenges arising from immunotherapy with pembrolizumab.

A 52-year-old female patient underwent a left nephrectomy and was diagnosed with poorly differentiated clear cell renal cell carcinoma (ccRCC) grade G4 stage T3N0M1 with iliac bone metastases. She was included in a clinical trial with pembrolizumab 400 mg every 6 weeks and belzutifan (an inhibitor of HIF-2α) 120 mg/day. The evaluation performed before the oncological treatment revealed normal liver functional tests (LFT), negative anti-HCV, negative HBsAg, positive total anti-HBc, positive anti-HBs (>1000 UI/ml) with a profile of cured hepatitis B. Five weeks after a single administration of pembrolizumab she developed jaundice, pruritus and abnormal LFT (week 0, Table I). It was considered as mixed pattern (hepatocellular and cholestatic: ALT=14.5 x ULN, ALP= 4.5 x ULN, GGT=10.5 x ULN, B=7.5 x ULN) checkpoint inhibitor induced liver injury - CHILI Grade 3 (according to Common Terminology Criteria for Adverse Events, Version 5.0). Pembrolizumab and belzutifan were discontinued; ursodeoxycholic acid (UDCA) (15 mg/kg/day; 750 mg/d) and immunosuppression (methylprednisolone 1 mg/kg/day - 48 mg/day and mycophenolate mofetil 1 g/d) was started. Despite immunosuppressive therapy, bilirubin increased to 12 mg/dl, and she was admitted to our institute (week 1, Table I). The history ruled out alcohol related liver disease, drug induced liver injury (DILI) and herbal induced liver injury (HILI). To date, Belzutifan (an inhibitor of HIF-2α) has not been implicated in significant liver toxicity, although transient and mild AST/ALT elevations were noticed in 20% of patients, but without jaundice and no need for drug discontinuation [2]. Autoimmune hepatitis panel was negative. No liver metastases, no dilations and no thickening of the bile ducts were evident in the contrast enhanced magnetic resonance imaging and magnetic resonance cholangiopancreatography. Viral hepatitis panel was negative for acute hepatitis A, C, cytomegalovirus, Epstein Barr virus, herpes simplex virus and without signs of B virus reactivation. Hepatitis E virus (HEV) IgM seropositivity raised the suspicion of acute hepatitis E and until the availability of the HEV RNA from serum and feces, Ribavirin was initiated (600 mg), mycophenolate was discontinued, and the dose of cortisone was tapered (week 1, Table I). HEV RNA was undetectable both in serum and feces, therefore acute hepatitis E was not confirmed – false seropositivity, and ribavirin was stopped. Tranjugular liver biopsy (week 2) provided a specimen for liver histology: mild portal inflammatory infiltrate with lymphocytes and neutrophils, focal lobular apoptosis, no lobular inflammation, no confluent necrosis, no malignant cells, negative staining for iron and copper, mixed intrahepatocellular and intracanalicular cholestasis in zone 3 and 2 (Fig. 1). The diagnosis was reconsidered as CHILI Grade 4 (bilirubin >10 x ULN), and according ASCO and ESMO guidelines the methylprednisolon dose was increased to 2 mg/kg/day (100 mg/d) [3, 4]. With UDCA therapy combined with intravenous 100 mg/day of methylprednisolone, bilirubin continued to increase, reaching 14 mg/dl and the case was declared as refractory hepatotoxicity. It was necessary to

Table I. The evolution of liver functional tests and the administered medication

Week	0	1	3	4	5	7	8	9	10	11	12	13	14	15
AST(xULN)	6.6	6.9	2.2	4.7	7	4	2.8	5.6	2.4	3	2.3	1.6	2.8	3.2
ALT(xULN)	14	14	4	11	22	14	8.8	6.6	6.9	6.3	4.7	2.8	3.8	5
ALP(xULN)	4.5	4	3	3	4.7	4.1	4.4	3.3	3.6	4.6	4	2.7	2.5	2.3
GGT(xULN)	10.5	10	11	27	52	37	43	34	40	39	36	21	14	11
B (xULN)	7.	7.5	10	11	12	7	6	3.3	2.4	2.3	2.2	1.6	1.3	1.3
Chol (mg/dl)	350						877	880		642	600	570	550	500
Medication														
MetP (mg/d)	48	↓	100	100	125	100	75	48	40	32	24	20	16	12
MMF (g/d)	1	-	-	1	1	1	1	1	1	1	1	1	1	1
UDCA (mg/d)	750	750	750	750	750	750	750	750	750	750	750	750	750	750
RBV (mg/d)	-	600	-	-	-	-	-	-	-	-	-	-	-	-
Fibrate (mg/d)	-	-	-	-	-	-	-	-	-	145	145	145	145	145
TKI (mg/d)	-	-	-	-	-	-	-	-	-	-	-	60	60	40

AST: aspartate aminotransferase (10-35 U/l); ALT: alanine aminotransferase (10-35 U/l), ALP: alkaline phosphatase (35-104 U/l); GGT- gamma-glutamyl transferase (5-36 U/l); B: total bilirubin (0.1-1.2 mg/dl); Chol: cholesterol (110-220 mg/dl), ULN-upper limit of normal: d: day, MetP: methylprednisolone (doses of 75, 100, 125 mg were given intravenously); MMF: mycophenolate mofetil; UDCA: ursodeoxycholic acid; RBV: ribavirin; Fibrate: fenofibrate; TKI: tyrosine kinase inhibitor - Cabozantinib, Week 0 : the onset of jaundice and abnormal LFT (liver functional tests)

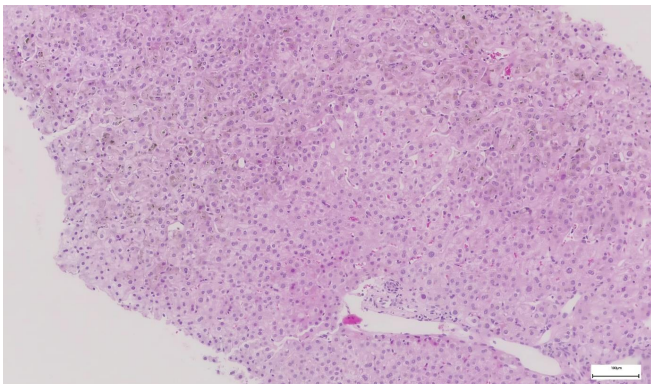

Fig. 1a. Hematoxylin-eosin staining. Portal space with mild inflammatory infiltrate

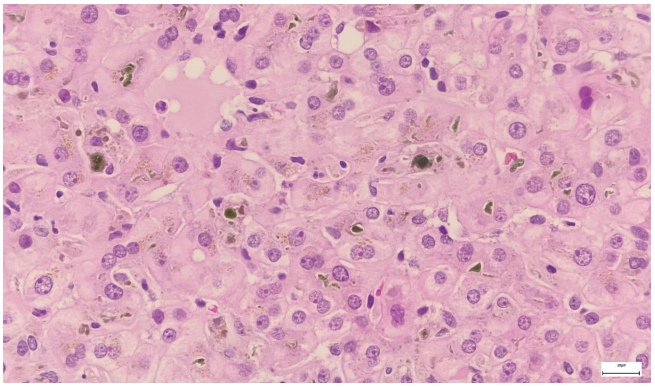

Fig. 1b. Magnification 40x. Prominent intrahepatocellular and intracanalicular cholestasis

increase the dose of methylprednisolone to 2.5 mg/kg/d (125 mg/d, intravenously) and to add a second immunomodulator agent - mycophenolate mofetil 1g/d (b.i.d). (Week 5, Table I). After two weeks, the bilirubin started to decrease significantly, and it has reached 7 x ULN. Although CHILI Grade 1 was not achieved, the tapering of the cortisone dose was started. The dose was reduced at the beginning by 25 mg/week and after reaching 48 mg/d the rate of tapering was switched to 8 mg/week and from the dose of 24 mg/d to a rate of 4 mg weekly (weeks 7-15, Table 1). At this moment, the patient is on a dose of 12 mg/d methylprednisolone and bilirubin reached 1.6 mg/dl. We estimate a duration of another 3 weeks of corticotherapy, and then the mycophenolate mofetil will be gradually reduced until discontinuation. UDCA and immunosuppressive therapy, even in maximum doses, did not influence pruritus, nor cholestasis liver enzymes, and cholesterol values reached very high values. Pruritus was favorably influenced by hydroxyzine therapy (2 x 25 mg/d). Cholestyramine was avoided due to the risk of interference with mycophenolate mofetil absorption. Statins are not recommended in severe cholestasis due to the increased risk of toxicity. Ezetimibe would be ineffective because the mechanism of hypercholesterolemia in cholestasis is not by increased cholesterol absorption. Off-label therapy with fenofibrate was introduced in week 11 and a moderate decrease of cholestasis enzymes and cholesterol was noticed, similar with the data published from other authors [6]. Meanwhile, new bone metastases appeared, and stereotactic radiotherapy of the lesions was performed. The resumption of oncological therapy was imperative. Most guidelines recommend permanent discontinuation of immune checkpoint inhibition following Grade 3 and 4 of CHILI, but in selected patients, immunotherapy may be resumed [7]. After balancing the risks of recurrent CHILI against the responsiveness of malignancy, it was decided the permanent discontinuation of the immunotherapy. Cabozantinib, a tyrosine kinase inhibitor was started in the 13th week, in order to control the malignancy. The dose was adjusted to the value of transaminases (Table I).

Pembrolizumab, acts as a checkpoint inhibitor (ICI) and is a humanized monoclonal antibody targeting the programmed cell death receptor-1 (PD-1). Since its approval in 2014, has demonstrated important clinical benefits in several forms of advanced/metastatic cancer but with the risk for immune related adverse events. The mechanism of liver injury is immunologically mediated; however, autoantibodies are usually not present and immunoglobulin levels are normal. There are activated CD8+ T cells directed at hepatocyte or cholangiocyte cell surface antigens giving the hepatocellular, cholestatic or mixed pattern of liver injury. Liver histology shows typically a panlobular hepatitis (focal or confluent necrosis with prominent lymphocytic infiltrates of activated T cells) and less often cholestatic liver injury (secondary form of sclerosing cholangitis or vanishing bile duct syndrome). Most immune related liver injuries (20 to 30%) are mild-to-moderate aminotransferase elevations and are usually self-limited. CHILI grade 2 and 3 occur in 1-4% of patients and lead to temporary ICI discontinuation. In 1% to 2% of patients, CHILI may be severe (grade 4) and even life threatening. The onset of CHILI typically occurs 8 to 12 weeks after ICI initiation, but there are cases reported as early as 8 days after treatment is commenced or as late as several months after therapy is completed. Most cases of hepatitis resolve in 1 to 3 months with immunosuppressive therapy (cortisone). Those with cholestatic forms of CHILI evolve in refractory cases even fatal. These require a higher dose of cortisone and the addition of an immunomodulator agent (mycophenolate mofetil, azathioprine, tacrolimus or antithymocyte globulin) [8].

Our case highlights the challenging diagnosis and treatment of CHILI. False HEV-IgM seropositivity delayed the initiation of the appropriate immunosuppressive therapy. The liver biopsy, although did not show the typical histologic lesions of pembrolizumab-related liver injuries, was important to rule-out an infiltrative malignancy. The response to combined immunosuppressive therapy was slowly favorable and required higher doses of methylprednisolone than those recommended in guidelines (2.5 mg/kg/d versus 2 mg/kg/d). The presence of metastases should not delay the early initiation of aggressive immunosuppressive therapy, as the persistence of abnormal LFT would hamper the resumption of oncologic therapy.

Adriana Cavași[1,2], Irina Știoleru[1], Maria Buziaș[1], Ioana Rusu[1]
1) Prof. Octavian Fodor, Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca; 2) Iuliu Hatieganu University of Gastroenterology and Hepatology, Cluj-Napoca, Romania

Correspondence: Adriana Cavași, adi.cavasi@gmail.com

Conflicts of interest: None.
DOI: 10.15403/jgld-5401

REFERENCES

1. Rădulescu L, Crișan D, Grapa C, Rădulescu D. Digestive toxicities secondary to immune checkpoint inhibition therapy – Reports of rare events. A systematic review. J Gastrointestin Liver Dis 2021;30:506-516. doi:10.15403/jgld-3671
2. Belzutifan In: LiverTox: Clinical and research information on drug-induced liver injury, [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/
3. Schneider B, Naidoo J, Santomasso B, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline update. J Clin Oncol 2021;39:4073-4126. doi:10.1200/JCO.21.01440
4. Haanen J, Obeid M, Spain L, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33:1217-1238. doi:10.1016/j.annonc.2022.10.001
5. Nemes K, Aberg F, Gylling H, Isoniemi H. Cholesterol metabolism in cholestatic liver disease and liver transplantation: From molecular mechanisms to clinical implications. World J Hepatol 2016;8:924-932. doi:10.4254/wjh.v8.i22.924
6. Carrion AF, Lindor KD, Levy C. Safety of fibrates in cholestatic liver diseases. Liver International 2021;41:1335-1343. doi:10.1111/liv.14871
7. Hountondji L, Ferreira De Matos C, Lebosse F, et al. Clinical pattern of checkpoint inhibitor-induced liver injury in a multicentre cohort. JHEP Rep 2023;5:1-12. doi:10.1016/j.jhepr.2023.100719
8. Pembrolizumab In: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/

Comparative evaluation of endoscopic variceal band ligation and carvedilol for prevention of first esophageal variceal bleed in high-risk cirrhotic patients

To the Editor,

Portal hypertension in cirrhosis is a leading cause of esophageal variceal bleed and mortality [1]. The incident bleeding increases the risk of risk of recurrent hemorrhage; therefore, emphasis should be put on primary prophylaxis in high-risk individuals [2]. The non-selective beta blockers (NSBBs) and the endoscopic band ligation (EVL) are both accepted methods for primary prophylaxis. However, the superiority of one over the other is not succinctly defined. While EVL has been successful in reduction of variceal bleed, however, it is invasive and requires discontinuation of prophylactic anti-coagulants which many of such patients are on. Additionally, it is expensive and risk of bleeding during banding can be fatal [3]. We aimed to compare the efficacy of Carvedilol, a NSBB with additional alpha blockade action which affects mesenteric circulation as well, with EVL for primary prevention of esophageal varices in high-risk patients.

To achieve this, we enrolled 52 high-risk cirrhosis patients with grade III/IV varices who did not have a history of prior variceal bleeding or use of beta-blocker therapy.

We excluded patients with co-morbid conditions that reduced life-expectancy, refractory ascites, and those who had the potential for adverse effects with beta blocker therapy. The subjects were randomized 1:1 into the EVL and Carvedilol groups (26 patients in each arm). The EVL group received the endoscopic intervention every 3 weeks until eradication, while the Carvedilol group was initiated on 6.25 mg/day, and the dose was doubled to 12.5mg/day if hypotension did not occur after one week of therapy. Follow-up was done at 1 week after Carvedilol initiation to assess safety, and thereafter both groups were assessed at 3, 6, 12 weeks, then at 6 months and 1 year. The primary and secondary endpoints included the first variceal hemorrhage and death, respectively.

The mean age in the EVL group was 55.15 ± 10.1 years, and 49.85 ± 8.1 years in the carvedilol group. The etiology for cirrhosis included alcohol [n=9 in both groups (34.6%)], hepatitis B virus [n=6 in both groups (23.1%)], hepatitis C virus [n=6 in both groups (23.1%)], and autoimmune and cryptogenic [n=4 in the EVL group (15.4%) and n=5 in the carvedilol group (19.2%)]. The history of hepatic encephalopathy was present in the EVL group (n=9, 34.6%) and carvedilol group (n=6, 23.1%). In the EVL group, 23.1% patients (n=6) had Child Pugh class A score, 61.5% had class B (n=16), and 15.4% had class C scoring (n=4). On the other hand, 23.1% class A (n=6), 57.7% class B (n=15), and 19.2% class C (n=5) comprised the Carvedilol arm. The causes of mortality in the EVL group (n=4, 15.4%) included variceal bleed (n=1, 3.8%), liver failure (n=1, 3.8%), infection (n=1, 3.8%), and cardiac cause (n=1, 3.8%). The mortality in the carvedilol arm (n=3, 11.5%) was associated with variceal bleed (n=1, 3.8%), liver failure (n=1, 3.8%), and infection (n=1, 3.8%). Adverse effects in the EVL arm included transient dysphagia (n=17), mild chest pain (n=7), and bleeding from post banding ulcer (n=2). The carvedilol arm had adverse effects of dyspnea (n=10), nausea (n=7), and hypotension requiring drug withdrawal (n=1). The

Table I. Comparative outcomes bleeding and mortality by the study time

	9 weeks	12 weeks	6 months	1 year	Total	p
Bleeding						
EVL, n (%)	1 (3.84)	4 (15.3)	5 (19.2)	5 (19.2)	5 (19.2)	0.41
Carvedilol, n (%)	0 (0)	1 (3.84)	2 (7.69)	2 (7.69)	2 (7.69)	
Mortality						
EVL, n (%)	1 (3.84)	2 (7.69)	3 (11.53)	4 (15.38)	4 (15.38)	0.99
Carvedilol, n (%)	0 (0)	1 (3.84)	3 (11.53)	3 (11.53)	3 (11.53)	

EVL: endoscopic band ligation for esophageal varices.

mean baseline hemodynamics for blood pressure (SBP/DBP) in EVL group was (129.15 ± 9.4)/(80.4 ± 2.8) mmHg and at end of 6 weeks, it was (124.4 ± 6.5)/(79.5 ± 2.6) mmHg. In the Carvedilol arm, baseline BP included (129.08 ± 8.044)/(81.3 ± 4.2) mmHg and (113 ± 9.5)/(74.8 ± 4.6) mmHg at weeks. Our study did not observe weight gain or worsening of ascites, which are known to occur with carvedilol.

Our results reflected lower bleeding rate in carvedilol arm compared to the EVL group, without a significant difference in mortality. Dose escalation for Carvedilol beyond 12.5 mg/day was refrained as prior studies suggest non-superior reduction with higher dose but are associated with increased adverse events.

The comparative studies on EVL and NSBBs have had conflicting results and superiority of one over the other is still debatable, and decision to choose the intervention depends on case-by-case basis. Carvedilol has been recognized to reduce portal pressure and thus prevent bleeding much better than other NSBBs like propranolol and nadolol(4). In addition to variceal bleeding, Carvedilol has shown to improve portal hypertensive gastropathy [5]. Our study elucidates that Carvedilol is well tolerated and shows similar or superior efficacy in primary prophylaxis. Our study aligns with the results by Tripathi et al. [6], thus adding rigor to our findings. Few studies showed non-superior but comparable results in for Carvedilol compared to EVL [7]. However, more data is required to compare efficacy. The significance of our findings includes comparable efficacy of Carvedilol, which offers additional benefits as well other than variceal bleed. Both interventions may not be suitable in patient-specific conditions such as use of anti-coagulants for EVL, risk of hypotension and orthostatic hypotension in elderly. In conclusion, Carvedilol is a safe and effective alternative to invasive and expensive EVL, which reduces costs and complications associated with the procedure.

Gadadhar Panda[1], Dhruv Ahuja[1], Suresh Kumar[1], Siddharth Srivastava[2], Premashis Kar[1]

1) Department of Medicine, Maulana Azad Medical College, Delhi University; 2) Department of Gastroenterology, Govind Ballabh Pant Institute of Postgraduate Medical Education and Research; India

Correspondence: Premashis Kar, premashishkar@gmail.com

Conflicts of interest: None.
DOI: 10.15403/jgld-4909

REFERENCES

1. McCormick PA, O'Keefe C. Improving prognosis following a first variceal haemorrhage over four decades. Gut 2001;49:682-685. doi:10.1136/gut.49.5.682
2. Graham DY, Smith JL. The course of patients after variceal hemorrhage. Gastroenterology 1981;80:800-809.
3. Lin HC, Soubrane O, Cailmail S, Lebrec D. Early chronic administration of propranolol reduces the severity of portal hypertension and portal-systemic shunts in conscious portal vein stenosed rats. J Hepatol 1991;13:213-219. doi:10.1016/0168-8278(91)90817-u
4. Stanley AJ, Therapondos G, Helmy A, Hayes PC. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. J Hepatol 1999;30:479-484. doi:10.1016/s0168-8278(99)80108-1
5. Tripathi D, Hayes PC. The role of carvedilol in the management of portal hypertension. Eur J Gastroenterol Hepatol 2010;22:905-911. doi:10.1097/MEG.0b013e3283367a99

COVID-19 as a possible cause for achalasia: a case report

To the Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel virus which caused a major pandemic [coronavirus disease 2019 (COVID-19)] and found to cause a respiratory illness [1]. Whilst transmission and presentation of COVID-19 was swiftly determined, pathophysiology mechanisms are still proposed [2]. COVID-19 enters the respiratory system through the angiotensin converting enzyme-2 (ACE2) receptor [3, 4]. Activation, proliferation, and infiltration of immune cells by cytokines occur following host invasion [3]. ACE2 receptors are found in respiratory, neurological, and gastrointestinal tissue; therefore, COVID-19 may present in various ways [3, 5]. Emerging literature describes possible mechanisms by which COVID-19 invades neurological tissue [6, 7]. Whilst there is significant scientific literature for the respiratory manifestation of COVID-19, less is known about the manifestation on other systems due to the variability of presentation. However, the loss of inhibitory neurons of the oesophageal myenteric plexus is a well-established mechanism of achalasia [8].

In August 2021, a 31-year-old female was referred for dysphagia to all consistencies and limb weakness after a recent COVID-19 infection. A contrast swallow showed significant dysmotility in the lower third of the oesophagus (Fig. 1a) with intra-oesophageal reflux and tertiary contractions. Following this, the patient underwent gastroscopy with normal biopsies.

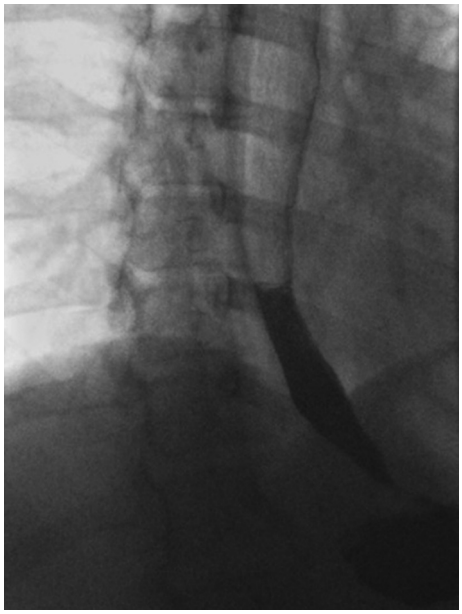

Fig. 1a. Achalasia: contrast swallow demonstrating significant dysmotility in the lower third of the oesophagus.

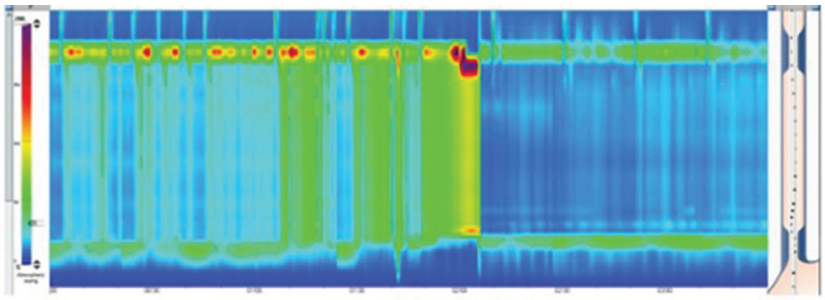

Fig. 1b. Achalasia: manometry result demonstrating type II achalasia.

Six months later, the patient had significant weight loss, worsening dysphagia and vomiting. The patient was admitted and underwent manometry, which diagnosed type 2 achalasia (Fig. 1b). The patient initially underwent oesophagoscopy and botulinum toxin injection for her achalasia, with little improvement. In August 2022, she underwent a laparoscopic Heller's myotomy and anterior fundoplication. Follow up after 4 months revealed a significant improvement in her dysphagia and weight gain back to her baseline.

Several publications describe the effect of COVID-19 on the nervous system [7, 8]; some cases suggest COVID-19 as a possible cause for achalasia. Zeidan et al. [9] report a 61-year-old male, treated for COVID-19 pneumonia; during the admission he developed new severe dysphagia as well as diarrhoea and significant weight loss. Investigations revealed type III achalasia [9]. Zeidan et al. [9] hypothesised that an inappropriate immune response to COVID-19 at the oesophagus caused degeneration of the inhibitory neurons at the myenteric plexus.

A further study assessed the lower oesophageal muscle of 7 patients diagnosed with COVID-19, compared with 10 patients without a COVID-19 diagnosis prior to surgery; the study found 6/7 of the COVID-19 positive patients had evidence of COVID-19 infection in the lower oesophageal muscle shown by immunohistochemistry demonstrated by heterogenous inflammatory infiltrates enriched with lymphocytes, scant polymorphonuclear leukocytes and scarce ganglion cells [10]. The findings from this study are also supported by work from Aponte et al. [11] who found increasing numbers (67.86% 19/28) of COVID-19 diagnosis in patients with achalasia.

The mechanism of neurological infiltration of COVID-19 proposed is similar to that of herpes zoster virus and influenza viruses [12, 13]. Some studies demonstrate neurological invasion of COVID-19 through the enteric nervous system by histochemical analysis on small intestine and large intestine, with post-mortem examination in COVID-19 positive patients [14, 15].

The literature mainly proposes two mechanisms by which COVID-19 may cause gastrointestinal symptoms. Firstly, a response in the lower oesophageal muscles, therefore causing oesophageal dysmotility and possible achalasia. The second mechanism is that of enteric plexus infiltration affecting the lower oesophagus, which is a known mechanism of achalasia [8]. There are limitations to this hypothesis, whilst a formal analysis of COVID-19 in the lower oesophageal muscles or myenteric plexus was not performed, the findings of this report are consistent with the increasing literature reporting COVID-19 as a possible cause for achalasia.

Mohammad Ahmad, Elizabeth Reynolds, Mahin Chowdhury, Mutwakil Abdalla, Simon Galloway
Department of Surgery, Manchester University Teaching Hospitals NHS Foundation Trust, Manchester, UK. 2School of Medicine, University of Manchester, Manchester, UK

Correspondence: Simon Galloway, simon.galloway@mft.nhs.uk

Conflicts of interest: None.
DOI: 10.15403/jgld-5062

REFERENCES

1. Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. Postgrad Med J 2021;97:312-320. doi:10.1136/postgradmedj-2020-138577
2. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J 2020;55:2000607. doi:10.1183/13993003.00607-2020
3. Cheung KS, Hung IFN, Chan PPY, et al. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. Gastroenterology 2020;159:81-95. doi:10.1053/j.gastro.2020.03.065
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-1242. doi:10.1001/jama.2020.2648
5. Casselbrant A, Edebo A, Hallersund P, et al. Angiotensin II receptors are expressed and functional in human esophageal mucosa. Am J Physiol Gastrointest Liver Physiol 2009;297:G1019-G1027. doi:10.1152/ajpgi.00255.2009
6. Wang F, Kream RM, Stefano GB. Long-Term Respiratory and Neurological Sequelae of COVID-19. Med Sci Monit 2020;26:e928996. doi:10.12659/MSM.928996
7. Aghagoli G, Gallo Marin B, Katchur NJ, et al. Neurological Involvement in COVID-19 and Potential Mechanisms: A Review. Neurocrit Care 2021;34:1062-1071. doi:10.1007/s12028-020-01049-4
8. Ruz Zafra P, Garcia Sanchez CJ, Perez Ramirez A, et al. Infection with SARS-CoV-2 as potential achalasia trigger. Rev Esp Enferm Dig 2023;115:203-204. doi:10.17235/reed.2022.8975/2022
9. Zeidan E, Desilets E, Bouin M, et al. A132 ACHALASIA FOLLOWING A SARS-COV-2 INFECTION: A CASE REPORT. J Can Assoc Gastroenterol. 2022;5:3-4.
10. Furuzawa-Carballeda J, Icaza-Chávez ME, Aguilar-León D, et al. Is the Sars-CoV-2 virus a possible trigger agent for the development of achalasia? Neurogastroenterol Motil 2023;35:e14502. doi:10.1111/nmo.14502

11. Aponte R, Daulabani N, Parra R, Perez Ybarra LM. Long COVID-19 and achalasia: a possible relationship? Int J Community Med Public Health 2022;9:2696-2700. doi:10.18203/2394-6040.ijcmph20221555
12. Khoury-Hanold W, Yordy B, Kong P, et al. Viral Spread to Enteric Neurons Links Genital HSV-1 Infection to Toxic Megacolon and Lethality. Cell Host Microbe 2016;19:788-799. doi:10.1016/j.chom.2016.05.008
13. Park CH, Ishinaka M, Takada A, et al. The invasion routes of neurovirulent A/Hong Kong/483/97 (H5N1) influenza virus into the central nervous system after respiratory infection in mice. Arch Virol 2002;147:1425-1436. doi:10.1007/s00705-001-0750-x
14. Marasco G, Lenti MV, Cremon C, et al. Implications of SARS-CoV-2 infection for neurogastroenterology. Neurogastroenterol Motil 2021;33:e14104. doi:10.1111/nmo.14104
15. Deffner F, Scharr M, Klingenstein S, et al. Histological evidence for the enteric nervous system and the choroid plexus as alternative routes of neuroinvasion by SARS-CoV2. Front Neuroanat 2020;14:596439. doi:10.3389/fnana.2020.596439

A biliary cast syndrome requiring liver transplantation: an original sequence

To the Editor,

Biliary cast syndrome (BCS) is a rare condition usually occurring after liver transplantation (LT) [1], but it has also been described in critically ill patients, then reported as sclerosing cholangitis in critically ill patients (SC-CIP). Biliary cast syndrome results from the aggregation of desquamation of the bile duct mucosa (supposedly after its necrosis following ischemia [2]) and bile (stones mainly containing bilirubin, collagen, and cholesterol [3]). Suspected on magnetic resonance imaging, the diagnosis is usually made by endoscopic retrograde cholangiography (ERCP), when identifying, and if possible, removing a typical tubular cast [2]. Biliary cast syndrome outcome is highly heterogeneous. In the most severe cases, a LT (or a re-transplantation) can be indicated; we report here a new case of a patient who underwent LT for BSC/SC-CIP.

A 61-year-old female patient with no medical history was first admitted in our institution in February 2022, and stayed 76 days in intensive care unit (ICU) for a septic shock related to peritonitis secondary to a perforated sigmoiditis. Initial laboratory findings were as follows: aspartate aminotransferase (AST) 132 U/l (normal: 10–45), alanine aminotransferase (ALT) 202 U/l (normal: 10–45), alkaline phosphatase (ALP) 777 U/l (normal: 38–120), gamma glutamyl transferase (GGT) 1672 U/l (normal: 7–65), direct bilirubin 6 µmol/l (normal: 0–20), C reactive protein (CRP) 312 mg/L (normal <5). Screening for viral or autoimmune liver disease was negative. The patient had no metabolic syndrome and did not drink alcohol in excess. The treatment consisted in a colectomy with Hartmann procedure, and the patient was discharged from surgery in April 2022. At that time, laboratory findings had significantly improved: AST 31 U/l, ALT 87 U/l, ALP 686 U/l (normal: 38–120), GGT 777 U/l, direct bilirubin 6 µmol/l (normal: 0–20). During this period, she presented several abdominal and pulmonary bacterial and fungal infections and received successively tazocillin, amoxicillin, vancomycin, cefepime, cotrimoxazole, imipenem/cilastatin, aztreonam, fluconazole and voriconazole. In addition, she presented a mild drug rash with eosinophilia and systemic symptoms (DRESS syndrome), resolutive with steroid therapy; it was hypothesized that persistent liver tests abnormalities were related to the DRESS syndrome. Liver ultrasound and CT scan were normal. In August 2022, the patient was re-admitted because of recurrent sepsis, due to Klebsiella pneumoniae and imipenem/cilastatin was re-introduced. Laboratory findings were as follows: AST 131 U/l, ALT 121 U/l, ALP 1572 U/l, GGT 1529 U/l, direct bilirubin 110 µmol/l, CRP 87 mg/L. A liver ultrasound revealed a diffuse mild biliary dilatation and a MRI cholangiography suspected a biliary cast, as a white hyper-intense intrahepatic images on non-enhanced T1-weighted and a "duct-in-duct" image (Fig. 1a) which was confirmed on subsequent ultrasound examination (Fig. 1b). These findings were consistent with the diagnosis of BCS. A liver biopsy was performed, showing only a mild steatosis (SAF score S3A1F2), without other damage. The first treatment consisted in an endoscopic retrograde cholangiography with extraction of endobiliary material confirming the BCS (Fig. 1c,1d). However, no significant decrease in the liver tests occurred, and a percutaneous biliary drainage was performed, to allow intensive saline solution flushing of biliary tree. After one month, again, no improvement was noted, and LT was considered. The day of LT, laboratory findings were AST 71 U/l, ALT 84 U/l, ALP 1378 U/l, GGT 556 U/l, direct bilirubin 110 µmol/l (normal: 0–20), CRP 44.3 mg/L (normal <5). The patient received antibiotics and antifungals during all the waiting period before LT.

Biliary cast syndrome pathogenesis is not clearly understood, but the mechanism mainly evoked is the consequence of bile duct mucosa necrosis following ischemia [2], whose squamous debris (underlined by the presence of collagen within stones), associated with bile components, mold biliary ducts [4] and lead to their obstruction, without major dilation of bile ducts on imaging. Associated superinfection and cholangitis could increase the phenomenon. In our case, the cause of BCS seems to have been the long stay in ICU, in a critically ill patient, resulting in biliary ischemia. The diagnosis is now most frequently made on MRI cholangiography as illustrated here, disclosing two signs, one sensitive represented by T1 hyperintense filling material (necrosed duct and sludge), and one specific the „duct-in-duct" image on T2-weighted sequences [1], corresponding to a true lumen compressed in the middle of cast material and a false lumen around the cast material in a dilated bile duct, and confirmed by ERCP. First step in BCS management is usually endoscopic or percutaneous radiological treatment by mechanical extraction of the stones. Successful endoscopic treatment is reported in only 25-60% of the cases [5] and percutaneous treatment does not seem to make better results, so it is sometimes necessary to perform surgical extraction of the stones. At last, if none of the precedingly cited treatment is efficient, a LT must be considered [3]. If no LT is performed, a rapid evolution to liver cirrhosis is possible [6] and survival rate is less than 50% one year after the diagnosis [2]. Nevertheless, early post-LT outcome is strongly

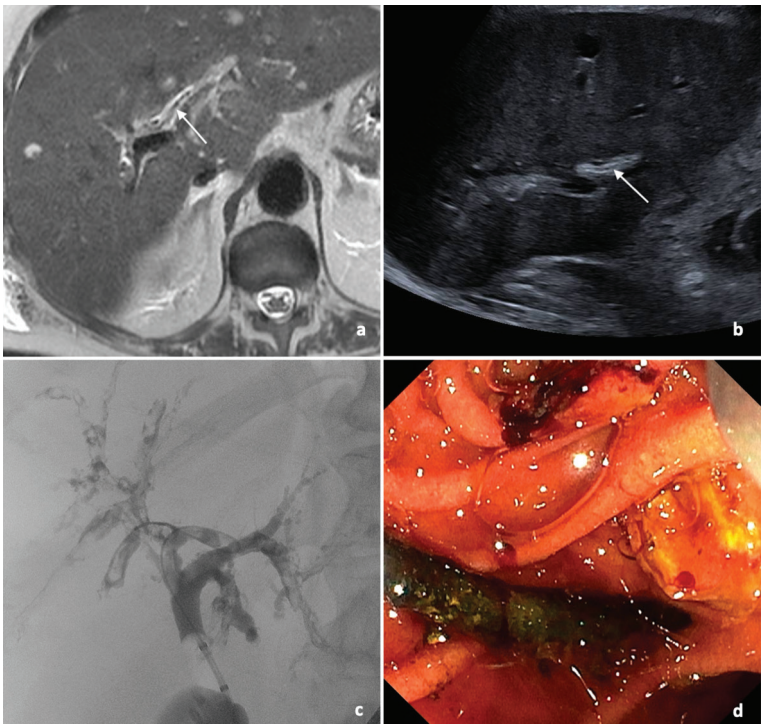

Fig. 1. a) MRI cholangiography: suspicion of a biliary cast, as a white hyper-intense intrahepatic images on non-enhanced T1-weighted and a "duct-in-duct" image (arrow): b) Ultrasonography: confirmation of a "duct-in-duct" image (arrow); c) Endoscopic retrograde cholangiography: multiple biliary casts in bile ducts: d) Biliary casts and stones extracted from bile ducts during endoscopic retrograde cholangiography.

impaired because of infectious complication, as illustrated by the series from Kirchner et al. [6] who reported that 6 of 18 BSC/SC-CIP patients died within 8 months after LT and the main cause of death was sepsis.

In conclusion, the diagnosis of BCS must be considered outside the context of LT, especially in critically ill patients with prolonged ICU stay, involving microcirculation disorders responsible for biliary ischemia. Liver transplant should be considered without delay, considering the difficulties of feasibility due to infectious complications.

Claire Michoud[1], Domitille Erard[2], Pierre-Jean Valette[3,4], Gaspard Bertrand[1], Thierry Ponchon[1,3], Laurent Milot[3,4], Jérôme Dumortier[1,3]

1) Hospices civils de Lyon, Hôpital Edouard Herriot, Fédération des Spécialités Digestives, Lyon; 2) Hospices civils de Lyon, Hôpital de la Croix-Rousse, Service d'Hépatologie, Lyon; 3) Université Claude Bernard Lyon 1, Lyon; 4) Hospices civils de Lyon, Hôpital Edouard Herriot, Fédération de Radiologie, Lyon, France.

Correspondence: Jérôme Dumortier, jerome.dumortier@chu-lyon.fr

Conflicts of interest: None.
DOI: 10.15403/jgld-5082

REFERENCES

1. Lemmers A, Pezzullo M, Hadefi A, et al. Biliary cast syndrome after liver transplantation: a cholangiographic evolution study. J Gastroenterol Hepatol 2021;36:1366–1377. doi:10.1111/jgh.15318
2. Kirchner GI, Rümmele P. Update on sclerosing cholangitis in critically ill patients. Visc Med 2015;31:178–184. doi:10.1159/000431031
3. Gor NV, Levy RM, Ahn J, et al. Biliary cast syndrome following liver transplantation: predictive factors and clinical outcomes. Liver Transpl 2008;14:1466–1472. doi:10.1002/lt.21492
4. Wang K, Wu S. Biliary Cast Syndrome. N Engl J Med 2020;382:e13. doi:10.1056/NEJMicm1909877
5. Paik WH, Lee SH, Ryu JK, et al. Long-term clinical outcomes of biliary cast syndrome in liver transplant recipients. Liver Transpl 2013;19:275–282. doi:10.1002/lt.23589
6. Kirchner GI, Hartl J, Schnitzbauer A, et al. 1929 Ischemic-like cholangiopathy with secondary sclerosing cholangitis: a good indication for liver transplantation? Transplantation 2012;94 (10S):419.

The diagnostic sensitivity of unprepared abdominal-pelvic computed tomography in high-risk patients for colonoscopy, suspected of colorectal cancer

To the Editor,

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths. Patients with suspected CRC and low anesthetic risk will proceed to colonoscopy, the current gold standard for tissue diagnosis with high sensitivity and specificity. However, there is a proportion of elderly, comorbid patients whose anesthetic risk precludes a colonoscopy [1]. Additionally, adverse outcomes including perforation and gastrointestinal bleeding may warrant an alternative method

for detection. A dedicated computed tomography (CT), colonography, has a sensitivity of 95% [2], like colonoscopy, but requires bowel prep which patients may not tolerate. CT colonography with oral contrast fecal tagging is another technique; however, identification of polyps is made more challenging by the lack of bowel preparation and thus sensitivity is expected to be lower at 72% [3]. Therefore, unprepared CT scan with intravenous contrast of the abdomen may be a simpler test to guide treatment in this high-risk patient group.

We aimed to evaluate the role of unprepared abdominal-pelvic CT in the work-up of colorectal cancer, given its favorable profile in patients deemed too high risk for a colonoscopy.

A retrospective single-center study was performed by conducting a search based on 'diagnosis-related groups' for colorectal cancer, subsequently cross-checked with the database of patients discharged from Colorectal/Gastroenterology units. We identified patients who underwent surgical resection for CRC who had a prior abdominal-pelvic CT with intravenous contrast. Indication for CT was pre-operative diagnostic work-up and performed within 6 months before surgery.

Patients were identified over a 9-year timeframe. Patients were excluded if they did not have a pre-operative CT, had imaging external to the hospital, or had a previous diagnosis of CRC. CT imaging reports were stratified based on a positive (tumor, mass, or bowel wall thickening) or negative diagnosis of cancer. Patients with a negative CT report underwent a secondary review by an independent sub-specialized radiologist.

507 patients met the inclusion criteria for this study. 39 patients were excluded, 15 had a previous CRC diagnosis, and 24 patients had non-CT pre-operative imaging. The sensitivity of abdominal pelvic CT after initial review was 0.87 (95%CI: 0.84-0.9, p<0.001) and 0.89 (95%CI: 0.86-0.92, p<0.001) after secondary review by a radiologist (Table I). 38 patients (0.07%) presented with a complete bowel obstruction due to CRC, verified on operation reports, and 100% of these were reported on the CTAP. There was no statistically significant difference in detection rates between left and right sided colon cancers on primary (p =0.89) or secondary review (p=0.91). Tumors detected on CTAP had a mean and median of 42 and 40 mm respectively compared to undetected tumors, which were 22 and 20mm respectively. Tumor size had a small but statistically significant effect on detection rate, with odds increasing 1.005 for every millimeter increase in tumor size.

Table I. Computed tomography findings on initial and secondary review

CT Finding	Tumour/ Mass	Obstructing Tumour	Malignant Stricture	Bowel wall thickening	Total
Initial review	265	38	1	136	440/507
Secondary review	267	38	1	142	448/507

We report a sensitivity of 87% of unprepared abdominal pelvic CT 87% for the detection of CRC in patients with high risk for colonoscopy; our result is slightly higher than the detection rate quoted by Klang et al [4]. As expected, tumor size was a significant predictor of detection, and CT was reliable in detecting obstructive tumors. The increase in detection rate following secondary review by a radiologist was previous reported [4, 5].

We are limited by the retrospective, single-center nature of our study. There may also be inherent bias of radiologists reading the initial scans, given they were performed as part of pre-operative staging and thus the presence of cancer was known. However, in real life situations, radiologists are also geared towards evaluating the bowel more closely if the clinical question posed was a suspected malignancy. Additionally, we evaluated abdominal pelvic CT with intravenous contrast only and thus cannot extrapolate our significant findings to non-contrast scans.

In conclusion, 87% of patients with CRC who underwent surgical resection had an abnormality that can be detected on unprepared abdominal pelvic CT with intravenous contrast. This certainly increases confidence in using CTAP with IV contrast as modality for screening for CRC in frail patients however adequate clinical suspicion and certain tumor characteristics need to be present for diagnosis.

Ashwin Patwardhan[1], Paul Simkin[2], Sourav Das[3], Annie Zhou[1], Geoff Hebbard[1,4]

1) Department of Gastroenterology and Hepatology, The Royal Melbourne Hospital, Parkville, Victoria; 2) Department of Radiology, The Royal Melbourne Hospital, Parkville, Victoria; 3) Melbourne EpiCentre, University of Melbourne and The Royal Melbourne Hospital, Parkville, Victoria; 4) Department of Medicine, University of Melbourne, Parkville, Victoria, Australia

Correspondence: Ashwin Patwardhan, ashwin.patwardhan@mh.org.au

Conflicts of interest: None.
DOI: 10.15403/jgld-5076

REFERENCES

1. Cha JM, Kozarek RA, La Selva D, et al. Risks and Benefits of Colonoscopy in Patients 90 Years or Older, Compared With Younger Patients. Clin Gastroenterol Hepatol 2016;14:80-86.e1. doi:10.1016/j.cgh.2015.06.036
2. Atkin W, Dadswell E, Wooldrage K, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. Lancet 2013;381:1194–1202. doi:10.1016/S0140-6736(12)62186-2
3. Rex DK. Fecal Tagging for CT Colonography. 2004 Nov 10. Retrieved from NEJM Journal Watch: Available from: https://www.jwatch.org/jg200411100000003/2004/11/10/fecal-tagging-ct-colonography
4. Klang E, Eifer M, Kopylov U, et al. Pitfalls in diagnosing colon cancer on abdominal CT. Clin Radiol 2017;72:858-863. doi:10.1016/j.crad.2017.06.007
5. Johnson CD, Flicek KT, Mead-Harvey C, Quillen JK. Strategies for improving colorectal cancer detection with routine computed tomography. Abdom Radiol (NY) 2023;48:1891-1899. doi:10.1007/s00261-023-03884-3