COVID-19 vaccinations in patients with chronic liver disease – experience of a tertiary centre in Melbourne

To the Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged onto the world stage in December 2019 and vaccinations became the became the gold standard that health officials utilised to slow viral spread. Chronic liver disease is associated with immune dysfunction with cirrhotic individuals more vulnerable to viral infections [1]. Despite this, this patient cohort is often plagued by poor medication adherence [2].

We performed a single centre cross-sectional study to evaluate the vaccination uptake and vaccine hesitancy in our cohort of patients. This study is part of an ongoing clinical audit to maintain standards of clinical practice in the Department of Gastroenterology, thus falling within the ethical parameters previously reviewed and approved by the Eastern Health Human Research and Ethics Committee on 29/03/2017.

We initially included 835 patients who attended Eastern Health Liver Clinic between 1/7/2021 - 30/9/2021. 237 were uncontactable and excluded, 598 were contacted by telephone and interviewed in clinic. 334/598 (56%) were male with a mean age of 54.35 years (IQR:23 years). 52% of patients were Caucasian, 19% North/Northeast/East Asian, 16% South/ Southeast Asian and the remainder were Middle Eastern (2%), European (6%) or other (3%). 87% were fully vaccinated (then considered ≥ 2 doses), and 1% had received a booster. 5% were unvaccinated and 5% received one dose only. Of the unvaccinated patients, 40% did not intend to get vaccinated and 23% refused to answer. Reasons reported for not getting vaccinated were safety concerns (39%), medical advice to abstain (36%) and doubts about efficacy (11%).

Ethnic background was significant (p=0.003) for vaccination rate using Chi-squared analysis, with patients of European background more likely to be unvaccinated (expected count 2:466, true count:8). Participants with alcoholic liver disease (expected count: 5.91, true count: 13) and hepatitis C (expected count: 1.389, true count: 3) were more likely to be unvaccinated (p=0.043). Patients with cirrhosis were also less likely to be vaccinated (p=0.011, expected count: 9.658, true count: 16), however there was no effect with decompensated liver failure. Of the 192 cirrhotic patients, 134 were asked whether they were aware of an increased risk of coronavirus disease 2019 (COVID-19) related complications, only 63 reported yes (47%).

COVID vaccination rates in our sample population appear to be significantly higher than that of the state as of 8/10/21 (87% vs 60%). However, this discrepancy may be explained by the rapid increase in COVID vaccination rates in the general population during the two months our study was conducted, up to 92% on 17/12/21 [3]. Furthermore, patients had to actively engage with the healthcare system to participate in our study which may have skewed the population captured.

Our observation that ethnic background having a significant effect on vaccination is congruent with a previous systemic review of vaccine acceptance rates [4], postulated to be due to cognitive, psychological, and sociocultural reasons present in Eastern European countries. Other social characteristics such as language spoken, socioeconomic status, gender and age were not associated with vaccination status.

Although our study showed that vaccination rates in liver clinic patients was higher than the general population, it is limited by small sample size and short time interval. However, our subset analysis indicates that cirrhotic patients had poor awareness of their at-risk status in the face of viral infections with lower vaccination rates and should be focused on by health practitioners broaching vaccinations. Future research should be done to investigate whether vaccine hesitancy extends to other vaccinations.

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Persistent abdominal pain in a patient with inactive Crohn's colitis: have you considered enteric dysmotility?

To the Editor,

A 43-year-old man was referred from another hospital due to persistent, disabling abdominal pain. The patient had a 10-year long history of Crohn's pancolitis, in deep remission for the last two years. He was previously extensively investigated, with blood chemistry, C-reactive protein, fecal calprotectin, repeated stool cultures, fecal examination for parasites/ova, upper gastrointestinal endoscopy with biopsies, ileo-colonoscopy with biopsies, intestinal ultrasonography, computed tomography enterography, and video capsule endoscopy, all showing normal or unremarkable findings. Treatment with mesalazine, 3.2 g/day, was stopped for a few months without affecting the characteristics of the pain. Since the patient did not fulfill the criteria for irritable bowel syndrome (IBS) and the pain significantly influenced his quality of life, he was referred to investigate a possible intestinal dysmotility by means of small bowel manometry [1].

On questioning, the patient reported that the pain started about eight months after the last disease flare, especially after meals, becoming progressively more frequent (about onetwo episodes per week in the last months) and intense [6 to 8 on a 10-point visual analog scale (VAS)], and unrelated to bowel movements (1-2 evacuations per day). No vomiting or (sub)obstructive episodes were reported. The patient also reported a deep decline of his quality of life, due to an anxiety state related to the uncertain nature of the pain. A duodenojejunal manometric examination (6 hours during fasting and 3 hours after a meal) was therefore carried out and analyzed according to previously described technique and methods [2]. Analysis of the tracing showed normal motility during fasting; in the post-prandial period, about 30 minutes and two hours after completion of the meal, duodenojejunal bursts of contractions with raising of the baseline, expression of enteric neuropathy [2], were documented (Fig. 1A and B), and were accompanied by abdominal pain like that complained of at home. Therapy with amitriptyline (50 mg t.i.d before meals) was prescribed, together with psychologic support. At three and six-months telephonic follow-up the patient reported considerable decrease of both frequency (on average, one episode per month) and intensity (2 to 4 on a 10-point VAS) of the abdominal pain, and his quality of life had considerably improved after discovering a cause for his symptoms.

Persistent abdominal pain in inflammatory bowel disease (IBD) patients after remission is a major clinical challenge since inflammation may "sensitize" the gut, leading to longlasting symptoms [3]. However, many such patients do not fulfill criteria for IBS, and complain mainly of persistent, often disabling abdominal pain, that impairs more or less profoundly their quality of life and whose origin is often



Fig. 1. Original tracing of duodenojejunal manometry, showing in both the early (A) and late (B) postprandial period the presence of bursts of contractions (defined as periods of >2 minute duration with continuous high amplitude (>20 mmHg) and high frequency (10-12/min) phasic pressure activity that were not propagated and not followed by motor quiescence; arrows) concomitant with abdominal pain (AP). The first six recoding points (spaced 2 cm apart) span the duodenum and the proximal jejunum, the last two (spaced 12 cm apart) are located in the mid-jejunum.

difficult to ascertain. It is worth noting that many patients with inactive Crohn's disease show gastrointestinal motor disorders, even though only a minority of them complain of mild symptoms [4]. In our case, an enteric dysmotility was documented. The latter is a condition difficult to diagnose and to treat, even because it often requires a manometric examination of the small bowel, not available in most centers. The pathophysiological mechanisms underlying enteric dysmotilities are still largely unknown; of interest, some studies suggest that the enteric nervous system may be compromised in these patients, even though to date no correlation has been found between pathological and manometric findings. The presence of persistent, disabling abdominal pain in patients with quiescent IBD, after investigation of common possible causes, should prompt the clinicians to consider alternatives including, where possible, the presence of abnormal motility conditions of the gastrointestinal tract. Finally, we want to stress the importance of trying to identify possible factors or triggers of abdominal pain in these subjects, according to the recent proposal of "treat-to-target" concept [5].

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Hepatitis B and hepatitis C seroprevalence among the blood donors in Pune, India

To the Editor,

Blood transfusion is a life-saving therapeutic intervention that is integral to management of diverse hematological and other diseases. Infectious agents including hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), malaria and syphilis continue to be the major threat associated with blood transfusion. Mandatory screening practices recommended by the WHO for donated blood have evidently reduced the risk of transmission of the above major transfusion transmissible infections (TTIs) in the past 20 years [1]; however, it still remains a challenge in the developing countries including India.

Highly infectious nature of HBV possessing relatively easy transmission routes from one infected person to another by blood contact, during birth, unprotected sex, sharing needles point towards greater risk of the disease [2]. Hepatitis C virus is a blood-borne pathogen transmitted by percutaneous membrane exposure to contagious blood. India has previously reported prevalence rates of 0.3%, 2% and 2%-8% for HIV, HCV and HBV respectively [3]. The current study aims to investigate the seroprevalence of hepatitis B and C viruses in the blood donors of Pune, Maharashtra, India.

The study population consisted of healthy blood donors who participated in the blood donation camps organized in Pune during January 2017 and October 2018. Blood donors who did not meet the exclusion criteria of age <18 or >65 years, history of long-term medication use, family history of liver disease, surgery, repeated blood donation within <1 year and pregnancy were excluded from the study. Serological tests for the detection of hepatitis B surface antigen (HBsAg), hepatitis B e-Antigen (HBeAg), antibody against the HBeAg antigen (anti-HBe) and antibody against HCV (anti-HCV) were performed. HBsAg and anti-HCV antibody positives were subjected to detection of HBV-DNA and HCV-RNA respectively, followed by viral load quantification and phylogenetic analysis.

A total of 3,881 donations were screened for HBV (n=3,282) and HCV (n=3,881) infections. Out of 3,881 study participants, 3,675 (94.7%) were males. The median age was 26 years (range: 18-65).

Twelve tested positive for HBsAg [11 males, 1 female, age in years, median (range) was 26 (18-42)] indicating an overall HBV prevalence of 0.36%. None of the HBsAg positive donors tested positive for HBeAg. However, 8/12 tested positive for anti-HBe antibody indicating possible cases of inactive chronic HBV infection.

Twelve tested positive for anti-HCV antibodies [10 males, 2 females, age in years, median (range) was 28 (19-37)] indicating a HCV prevalence of 0.31%. Gender wise, HBsAg and anti-HCV seropositivity was comparable. The age-specific distribution of HBV and anti-HCV antibodies revealed a higher prevalence within the age group of >40 years (HBV: 1.04%, HCV: 4.17%). HBV-DNA viral load detected in 8 viremic donors ranged between <250 and 7.4x10⁴ copies/



Fig. 1. Phylogenetic analysis of the sequences obtained from HBV DNA positive blood donors. The tree was constructed using Kimura 2 parameter distance model and neighbor-joining method available in MEGA 6.06 software. Bootstrap values are given as a percentage of 1000 replicates. Sequences detected in this study are indicated by black dots. Representative sequences of different HBV genotypes have been included in the tree.

mL. Phylogenetic analysis revealed Genotype D to be the most prevalent (7/8, 87.5%). The 8 sequences obtained from HBV DNA positive donors (GenBank accession numbers: ON791841–ON791848) aligned with sequences of different HBV isolates submitted in GenBank with identity percentage ranging between 99.44% and 100% (Fig. 1). None of the samples tested positive for HCV-RNA.

The current seroprevalence of HBV (0.36%) and HCV (0.31%) among blood donors is in line with studies on blood donors from some other countries across the world (HBV prevalence: 0.007% - 25%, HCV prevalence: 0.06% - 1.7%) [4-5].

The observed higher seroprevalence of HBV and HCV in the age group of >40 years compared to the young donors

may be associated with increased exposure to HBV/HCV and may point towards different risk behaviors in this age group.

In conclusion, despite stringent donor screening and testing practices, safe blood free from TTIs remains an elusive goal. Sensitive screening methods, pre-donation counseling and recruitment of regular donors are important to ensure blood safety for the recipients.

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ADA-2 gene mutation in a Crohn's disease patient without response to therapy

To the Editor,

We read the comprehensive paper about association between responses of the therapy and certain genetic expression in patients with inflammatory bowel diseases by Tarapatzi et al. [1], published recently in Journal of Gastrointestinal and Liver Diseases. Crohn's disease (CD) is an inflammatory disorder of uncertain etiology that is characterized by transmural inflammation in the gastrointestinal tract and can result in severe morbidity and reduced quality of life [2]. We present a patient with CD who did not respond to induction of remission and was found to have a likely pathogenic mutation in the adenosine deaminase-2 (ADA-2) gene, despite any clinical manifestations of deficiency of adenosine deaminase 2 (DAD2). It may be associated with resistance to CD treatment or prognosis of CD. This is the first reported case of an association between DAD2 and CD.

A 20-year-old female was initially investigated for abdominal pain for 3 months and diarrhea for 2 weeks, happening 6-7 times a day without blood. The patient was diagnosed with CD in September 2021, following a colonoscopy with biopsy. The histopathological results were leukocyte accumulation and granulation tissue with distorted crypt architecture. The initial CD Activity Index (CDAI) was 394. The Montreal classification was A2L2B1. The initial treatment regimen included prednisolone (32 mg), mesalazine (3.2 g orally and 4 g rectally), and azathioprine 150 mg. However, the patient did not achieve induction remission with this therapy. Subsequently, the patient received 5 doses of intravenously infliximab, 300 mg each month. Intravenously vedolizumab therapy, 300 mg, was initiated because of no response to infliximab. In October 2023, the CDAI was 263. During the grand visit in February 2023, the patient's progress was discussed, and it was decided to perform Familial Mediterranean fever (FMF) and primary immune deficiency (PID) gene analysis for differential diagnosis of CD. Ustekinumab, administered subcutaneously at a dose of 90 mg every 8 weeks. After completing the first 3 doses of ustekinumab in August 2023, the patient's CDAI was 458 (Fig 1).



Fig. 1. Timeline of treatments.

For differential diagnosis, infectious colitis was excluded by stool analysis and celiac disease by negative serology (Supplementary file). Rheumatological diseases were excluded by biomarkers. There were no significant mutations in FMF gene analysis.

At the same time, PID gene analysis was completed, which revealed a heterozygous and likely pathogenic mutation in the ADA-2 gene (R49Afs*13). The patient did not exhibit any clinical manifestations of DAD2, such as vasculitis or hematologic or immunological presentations. Activity of ADA enzyme was resulted as 2,7 U/L. For differential diagnosis of common variable immunodeficiency, serum immunoglobulin levels were found to be within normal range. No significant results were found in analysis of lymphocyte subgroups and the titers anti A1 and B were negative.

The advent of advanced technology has facilitated the widespread use of promising genetic techniques, such as whole genome sequencing and whole-exome sequencing, which have led to the identification of approximately 200 IBD risk loci. Particularly for CD, specific genes, namely NOD2 and ATG16L1, had the highest risk [3]. Certain subtypes of PID can present with Crohn's-like symptoms. ADA gene mutations in the PID gene are highly linked to ulcerative colitis and very early onset inflammatory bowel disease [4]. There is no evidence to indicate that an association between the ADA gene and CD has a typical presentation, according to current research.

The clinical manifestations of DAD2 range from abdominal pain to stroke. The association between CD and ADA-2 gene mutations has not been observed in recent research. This is the first case on this topic in the literature. The development in precision medicine over years will make this crucial for CD patients who are not in remission.

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Bridging the angle: a case report on superior mesenteric artery syndrome

To the Editor,

Superior mesenteric artery syndrome (SMAS), also named Wilkie syndrome, is a disorder of the gastroenteric vascular system in which the third part of the duodenum is compressed posteriorly by the abdominal aorta and anteriorly by the superior mesenteric artery by its acute angulation [1]. It was initially identified by Carl Freiherr von Rokitansky in post-mortem examinations in 1861, remained unofficially characterized until 1927 when Sir David Percival Dalbreck Wilkie published a series of studies involving 75 patients [2]. The reported prevalence of SMAS is often low, and it is estimated to occur in a small percentage of the population. Prevalence figures may range from 0.1% to 0.3%, but these numbers can be influenced by factors such as the criteria used for diagnosis, the population studied, and geographic variations [3].

We present a case of a 30-year-old woman presenting with discernible epigastric discomfort, precipitated by early satiety following ingestion of both liquids and solids, accompanied by episodes of nausea and vomiting. The symptoms initially started 9 months prior to presentation and worsened within the last 48 hours. The patient described the pain as intermittent and colicky, during which no remedial measures were undertaken at home. An in-depth exploration of the patient's medical history unveiled a concomitant involuntary weight loss of 7 kilograms since the onset of symptoms, coupled with recurrent bouts of abdominal pain, for which she sought recourse from her family physician.

Upon clinical examination, the patient was found to have tenderness in the epigastrium and left hypochondrium, with excess borborygmi upon abdominal auscultation. Routine labs revealed a mildly elevated C-reactive protein, in addition to low iron and vitamin B12 levels. Abdominal ultrasound showed thickening of the gastric wall and presence of post-prandial contents. Contrast-enhanced computed tomography (CT) of the abdomen showed an aortomesenteric angle of 21.2 degrees (Fig. 1a) and an aortomesenteric distance of 5.11 mm to the right of the left renal vein and 8 mm to the right of the 3rd segment of the duodenum (Fig. 1b), confirming the diagnosis of superior mesenteric artery syndrome.



Fig. 1a. An aortomesenteric angle of 21.2 degrees was found on contrast-enhanced CT of the abdomen.



Fig. 1b. Contrast-enhanced CT of the abdomen showed an aortomesenteric distance of 5.11 mm to the right of the left renal vein and 8 mm to the right of the 3rd segment of the duodenum.

The patient received in-patient care, conservatively, over the course of 3 days with antispasmodics, NSAID's for pain, prokinetics for nausea, and rehydration therapy. The patient was also instructed to remain nil per os (NPO) for the first day of hospitalization until abdominal ultrasound was performed to re-evaluate if gastric contents have been emptied, after which small meals were introduced with posture therapy (left lateral decubitus). Surgical intervention was not needed as ingestion of solids and liquids were possible without pain, nausea/vomiting, or early satiety. The patient was then discharged and instructed to follow-up in the out-patient clinic.

In our case, the chronicity of symptoms, coupled with weight loss and abnormal laboratory findings, prompted a thorough investigation, leading to a definitive diagnosis by abdominal contrast-enhanced CT. Diagnosis hinges on a comprehensive evaluation of clinical symptoms and radiological imaging, such as CT scans and barium studies, revealing obstructive patterns. In modern day medical imaging, normal ranges of the aortomesenteric angle are between 38 to 65 degrees, with an aortomesenteric distance of 10 to 28 mm. These parameters are reduced in cases of superior mesenteric artery syndrome, with typical measurements revealing an aortomesenteric angle between 6 to 22 degrees and an aortomesenteric distance ranging from 2 to 8 mm [4].

The patient's successful three-day in-hospital management, involving conservative measures such as antispasmodics, NSAIDs, prokinetics, and rehydration therapy, obviated the need for surgical intervention. The decision to keep the patient NPO initially, followed by small meals with posture therapy, effectively alleviated symptoms. Discharge with a follow-up plan acknowledges the chronic nature of SMAS, highlighting the evolving trend towards non-surgical interventions in its management. While conservative measures are typically the initial line of treatment, certain emergent cases necessitate prompt surgical intervention upon admission to the emergency department [5, 6].

This case contributes to the limited literature on SMAS, emphasizing the importance of comprehensive diagnostic approaches and the potential success of conservative measures in selected cases. Ongoing research and increased awareness will further refine diagnostic criteria and optimize therapeutic strategies for this rare but clinically significant syndrome.

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Prone position vs. left lateral decubitus position in endoscopic retrograde cholangiopancreatography: a meta-analysis

Table I Demographic data of included patients IR EPCP indication

To the Editor

Endoscopic retrograde cholangiopancreatography (ERCP) is most commonly performed in the prone position. Although the prone position is ideal for endoscopists, it is not optimal for all patients. The left lateral position is an alternative but adversely affects the fluoroscopic visualization of the left and right hepatic ducts and the pancreatic duct [1]. We compared the safety and efficacy of the prone and left lateral positions for ERCP.

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for our study. We searched databases, including PubMed, Scopus, Web of Science, and Cochrane CENTRAL, until March 2022, for studies meeting the eligibility criteria. We utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Guidelines. The risk of bias assessment of included trials was conducted using Cochrane's risk of bias tool. The observational study was assessed according to the National Heart, Lung, and Blood Institute (NHLB) tool. We analyzed continuous and dichotomous data using mean difference (MD) and risk ratio (RR), respectively, and a 95% confidence interval (CI). The data were analyzed using a fixed-effects model and a random-effects model. Heterogeneity was measured using I² and the p-value of the Chi-square tests. The p values < 0.1 or I^2 > 50% represented significant heterogeneity. The inconsistency of heterogeneous outcomes was resolved performing subgroup analysis according to the duration of treatment or Cochrane's leave-one-out method.

Four studies including 1026 patients (617 prone, 409 supine) were included [1-4] (Table I). The quality assessment yielded an overall low risk of bias according to Cochrane's risk of bias tool. All trials were categorized as having a low risk of bias.

For biliary cannulation success 964 patients were assessed [2-4]. The success rate was lower with left lateral decubitus position than with prone position (RR=1.06; 95%CI: 1.03-1.10), (p=0.004). Pooled analysis revealed heterogenity (p=0.05; I^2 =67%) (Fig. 1A). We solved the heterogeneity (p=0.66; I^2 =0%) by using random effects and excluding Verma

Tuble 1. Demographic data of included patents, ib. ENOT indications													
STUDY	Sample Size		Duration of the study		Age (years) mean (SD)		Males (n)		Females (n)		BMI. mean (SD)		
	Prone	LLD			Prone	LLD	Prone	LLD	Prone	LLD	Prone	LLD	
Batheja 2013	39	20	2009 to 2010		63(15)	64 (17)	17	9	22	11	NR	NR	
Alcivar-Leon 2017	426	226	2013 to 2017		56	60	202	102	224	124	NR	NR	
Park 2017	31	31	2015 to 2	2016	62 (17.1)	65,2 (15.9)	19	13	12	18	25.5 (3.5)	24 (3.2)	
Verma 2019	121	132	2017 to 2	2018	65.4 (18.2)	66.7 (17.4)	55	64	66	68	NR	NR	
STUDY	ERCP in	ERCP indications											
	Choledocholithiasis, n (%)		Mali	Malignant stricture, n (%)		Benign stricture, n (%)		Others, n (%)					
	Prone	LL	LLD		e LL	D	Prone LLD			Prone	LL	LLD	
Batheja 2013	16 (41)	11	11 (55)		.) 5 (25)	3 (8) 1 (5)			12 (31)	3 (3 (15)	
Alcivar-Leon 2017	NR	NR		NR	NF	ł	NR	NR		NR	NI	NR	
Park 2017	13 (41.9	13 (41.9) 18 (58.1)		6 (19	9.4) 6 (19.4)	7 (2.6) 2 (6		5)	4 (12.9)	5 (16.1)		
Verma 2019	93 (76.9	93 (76.9) 88 (66.7)		10 (8	3.3) 27	(20.5)	1 (0.8)	39 (2.3)		16 (13.2)		(10.7)	

LLD: left lateral decubitus position; NR: not reported; BMI: body mass index; SD: standard deviation.



Fig. 1. Forest plots for Biliary Cannulation and Ampullary Localization Time (A-C)

et al. [3]. After solving the heterogeneity, the success rate was still lower in the left lateral decubitus position group than in prone position group (RR=1.08; 95%CI: 1.03-1.14, p=0.001) (Fig. 1B).

Regarding the overall adverse events, there was no difference between groups (RR=0.79; 95%CI: 0.59-1.06, p=0.12). Data were homogenous (p=0.60, $I^2=0$ %).

Two studies reported pancreatitis outcomes [1, 3]. Our analysis yielded no variation between both groups (RR=1.36; 95%CI: 0.61-3.06, p=0.45). The combined analysis was homogeneous (p=0.18, I^2 =43%).

Two studies assessed bleeding outcomes [1, 3]. There was no difference between both groups (RR=1.02; 95%CI: 0.34-3.01, p=0.98). Pooled analysis was homogeneous (p=0.48, I^2 =0%). For cardiopulmonary events 314 patients were assessed. The overall risk ratio showed no difference between both positions (RR=1.06, 95%CI: 0.35-3.23 p=0.92). Data were homogenous (p=0.56; I^2 =0%).

Procedure time was evaluated in two studies [1, 3]. The overall mean difference did not favor either position (MD=-1.08; 95%CI: -3.79-+1.62, p=0.43). Pooled analysis was homogeneous (p=0.56, I^2 =0%).

For ampullary localization time (mins) 377 patients were analyzed [1, 2, 4]. The combined mean difference favored the prone group (MD=-0.52, 95%CI:-1.01 - -0.02, p=0.04). Pooled analysis was homogenous (p=0.78, I^2 =0%) (Fig. 1 C).

The main limitations of this meta-analysis were the small number of included trials and the heterogeneity between the trials [1-4]. Overall, our analysis favors the prone position over the left lateral position for ERCP.

In conclusion, prone position was associated with a higher rate of successful common bile duct cannulation than prone position and shorter ampullary localization time. There was no significant variation between the two positions regarding the time of the procedure. Also, we found no difference between the two positions in adverse events including bleeding, cardiopulmonary events, and pancreatitis.

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