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Outcomes of Endoscopic Ultrasound-guided Gastroenterostomy Using Lumen-apposing Metal Stent in the Treatment of Malignant and Benign Gastric Outlet Obstruction: A Case Series

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ABSTRACT

Objective: To study the outcomes of endoscopic ultrasound-guided gastroenterostomy (EUS-GE) using lumen-apposing metal stent (LAMS) in patients with benign and malignant gastric outlet obstruction (GOO).

Materials and Methods: This single-center study retrospectively reviewed the medical records of benign and malignant GOO patients who underwent EUS-GE between May 2019 and September 2023. We evaluated the technical success, adverse events related to the techniques used, clinical success, and recurrence and reintervention rates.

Results: A total of twelve patients who underwent three different EUS-GE techniques were included in this study. The first method was the direct over-the-guidewire technique, the second was the wireless-freehand method, and the third was modified endoscopic ultrasound-guided double-balloon occluded gastroenterostomy bypass (M-EPASS). All 3 techniques used preloaded oroenteral catheters in combination. Technical success was achieved in 83.3% (10/12) of patients, and there were 16.6% (2/12) failures due to misdeployment. One (8.3%) severe adverse event occurred resulting in peritonitis during the direct over-the-guidewire method. The second failure, which ensued after use of the wireless-freehand technique, achieved successful stent deployment at the second attempt without any complications. Clinical success was 100% (11/11), and mean follow up was 6.2 months. There was one (9.1 %) incidence of recurrence at 12-month follow up.

Conclusion: EUS-GE is effective in the management of GOO, and the wireless-freehand and M-EPASS techniques in combination with oroenteral catheters should be the technique of choice in term of safety and efficacy.

Keywords: EUS-guided gastroenterostomy; lumen-apposing metal stent; gastric outlet obstruction; benign; malignant
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INTRODUCTION

Endoscopic ultrasound-guided gastroenterostomy (EUS-GE) using lumen-apposing metal stent (LAMS) has been used as an alternative treatment for malignant gastric outlet obstruction (GOO). It has been shown by many studies to achieve good clinical outcomes and to result in fewer complications compared to surgical gastrojejunostomy; furthermore, it requires less reintervention compared to endoscopic enteral stenting. Recent publications have investigated the use of this procedure for the treatment of benign GOO and reported similar outcomes. However, the technical success and adverse events reported in many studies still vary, probably because of the use of various unstandardized techniques, the different equipment utilized for the procedure in each center, and the small number of patients in most of the studies. With regard

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to benign GOO, data is still limited with respect to long-term placement of the stent and attendant complications, the need for a stent, and the proper timing of its removal. Our study retrospectively reviewed the use of EUS-GE in malignant and benign GOO using electrocautery-enhanced LAMS in order to investigate its outcomes in terms of technical success, adverse events following each technique, clinical success, and recurrence and reintervention rates at long-term follow up.

MATERIALS AND METHODS

This research was approved by the Institutional Review Board (code:66164). The medical records were retrospectively reviewed of individuals who underwent EUS-GE between May 2019 and September 2023, and 12 patients were included in the study. The nature of the GOO was confirmed by the results of esophagogastroduodenoscopy (EGD) and/or abdominal CT scan, with GOO score of 0-1 (Table 1).[1] The inclusion criteria for malignant obstruction were unresectable diseases and benign GOO unfit for surgery. The exclusion criteria were massive ascites.

All patients underwent general anesthesia or deep sedation with propofol, and antibiotic prophylaxis was administered preoperatively. The procedures were performed using a 15x10 mm. or 20x10 mm in diameter LAMS with electrocautery-enhanced delivery system called Hot AXIOSTM Stent (Boston Scientific Corp., Marlborough, MA, United States) which facilitated trans-gastric puncture and stent deployment in a single step.

The technical steps of EUS-GE.

Gastroscopy with gastric irrigation was performed prior to starting EUS-GE with the aim of eliminating gastric content. Preloaded devices included nasobiliary tube; balloon catheter for stone extraction or nasojejunal tube feeding over the 0.025 or 0.035-inch guidewire beyond the tumor; and an oroenteral tube with an endoscopy irrigation pump to continuously infuse the mixed solution of normal saline combined with contrast medium and a small amount of blue dye, such as indigo carmine or methylene blue, during the EUS-GE procedure in order to facilitate the visualization of enteral segment by EUS. One of three EUS-GE techniques was then employed.

Direct EUS-GE over-the-guidewire technique: After continuously infusing the mixed solution into the targeted enteral loop via an oroenteral catheter, as described previously, the target intestinal loop was identified under EUS and fluoroscopy. After this, a transgastric puncture of the loop was performed using a 19 G needle, followed by fluid aspiration using blue dye to confirm that the correct intestinal loop was aspirated, and then a 0.025inch guidewire was placed into the small bowel. The needle was exchanged for the LAMS with an electrocautery-enhanced delivery system which was then advanced from the stomach through the target intestinal loop while applying cautery using the ERBE (ERBE Elektromedizin GmbH; Tübingen, Germany) with electrocautery setting (Effect 5; 100 W Autocut) over the guidewire. The distal flange was deployed under EUS vision and pulled back until it was close to the wall of the targeted enteral loop, and the proximal flange was positioned intra-channel of the echoendoscope before being pushed away from the scope under endoscopic vision.

Wireless-freehand insertion technique: After the target enteral loop was identified using the technique described earlier, the LAMS with electrocautery-enhanced delivery system was advanced and then deployed in the same maneuver without placement of any guidewire.

Modified endoscopic ultrasound-guided double-balloon occluded gastroenterostomy bypass (M-EPASS): After placing a balloon for stone extraction via an oroenteral catheter, an additional stent graft balloon catheter such as ReliantTM stent graft balloon catheter (Medtronic) or the Coda® balloon catheter (Cook Incorporated, Bloomington, IN) was advanced over a 0.025 or 0.035-inch guidewire and positioned at the ligament of Treitz for temporary occlusion of the duodeno-jejunal segment to prevent rapid draining of the infused fluid from affecting the prolonged visualization of the target enteral loop in order to facilitate the EUS-GE procedure (Fig 1 & 2). The LAMS with electrocautery-enhanced delivery system was then deployed using the wireless-freehand technique.

After the LAMS was deployed, the correct position of the stent was confirmed by passing the mixed solution through the stent into the gastric lumen. All patients were allowed a fluid diet the day after the procedure if

TABLE 1. The gastric outlet obstruction scoring system

Level of oral intake	Score
No oral intake	0
Liquids only	1
Soft solids	2
Low-residue or full diet	3

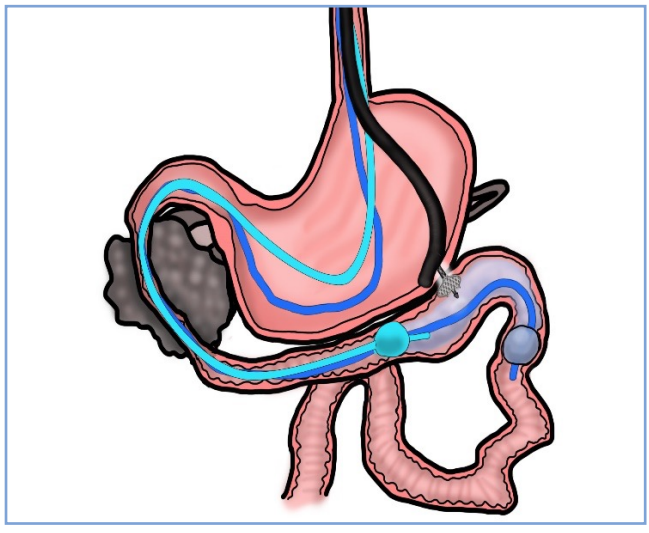

Fig 1. Double balloon catheter technique

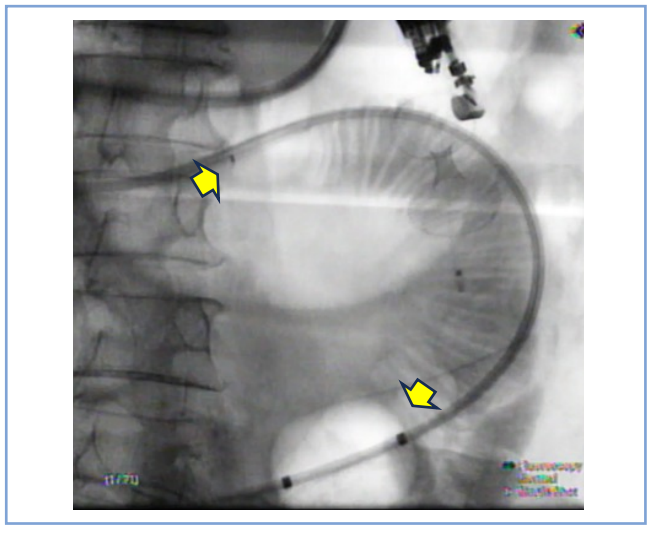

Fig 2. Double balloon catheter technique: the balloon extraction catheter and stent graft balloon catheter (arrows)

Medical illustrator: Tanyaporn Chantarojanasiri, M.D.

no signs of perioperative complications were observed, and they progressed to a full diet on the following day.

Technical success was defined as the correct positioning of the stent deployment. Adverse events were recorded as perforation, bleeding, peritonitis, and cardiopulmonary adverse events from sedation. Clinical success was defined as improvement in GOO score from 0-1 to 2-3. Recurrence was defined as a decrease in the GOO score to 0-1 after earlier improvement.

RESULTS

A total of 12 consecutive patients underwent EUS-GE. Their mean age was 57.8 years (range 30-82 years), and 10 of them were female. Nine had malignant etiologies, 2 had benign conditions, and one had an uncertain diagnosis. The majority of the obstructions were located at the 1st-3rd parts of the duodenum with two cases of pyloric obstruction. Preoperative GOO scores were 0-1, and the duration of the presence of obstruction varied from 0.5-6 months (Table 2).

All patients successfully demonstrated enteral segment after preloading of an oroenteral catheter and continuous infusion of the mixed solution. Ten patients had technical success (Table 3). The first technical failure occurred as a result of misdeployment of the first flange into the peritoneal cavity, after which the patient developed peritonitis immediately, probably due to improper preoperative stomach preparation resulting in severe contamination of the abdominal cavity. She underwent laparotomy in order to decontaminate the infected material and then had surgical gastrojejunostomy. She had a good recovery and was discharged about a week later. The second technical failure (patient No.9) had stent misdeployment at the first attempt under the wireless-free hand technique, but a stent was successfully deployed at the second attempt using the same technique in the same session after endoscopic closure of the gastric defect had been performed with a clip, and no peritonitis developed. In summary, the technical success of the wireless-freehand technique was 75% (3/4), while the M-EPASS approach achieved 100% (6/6), and the overall technical success was 83.3% (10/12). Unfortunately, one success was achieved with an unknown technique because no data were recorded, while the direct over-the-guidewire technique achieved no technical success 0% (0/1).

All eleven patients who successfully received EUS-GE attended final follow up at a mean of 6.2 months (range 0.75-22 months), and they all achieved clinical success and had improved their GOO score to 2-3. The longest stent patency was recorded at 20 months with a 10x20 mm diameter stent. Only one patient (patient number 2) developed recurrent obstructive symptoms from tissue ingrowth, with decreased GOO score down to 0 at the 12-month follow up after also receiving a 10x20 mm diameter stent. After failing to respond to endoscopic balloon dilation, he received an additional LAMS size 10x20 mm (stent in stent) with the use of a therapeutic gastroscope after the tissue ingrowth was burned using forced argon plasma coagulation of 60 watts. The stent patency was observed endoscopically and intraoperative contrast medium from the gastric site was found to have passed through the stent into the jejunum (Fig 3). The patient had good response with GOO score 3 at the last 5-month follow up. The patient with SMA syndrome (patient number 11) had endoscopic stent removal after 5-month follow up and regained weight. Contrast study showed improvement in the duodenal obstruction, and there were no adverse events during stent removal.

TABLE 2. Patient characteristics

Patient	Age	Gender	Co-morbidities	Etiology of GOO	Location of obstruction	Duration of obstruction (months)	Pre-operative GOO score
1	72	Female	CHF	Peptic stricture	Pylorus	2	1
2	30	Male	None	Hilar cholangiocarcinoma	1st-2nd part duodenum	5	0
3	56	Female	None	Carcinoma of the uncinate process of the pancreas	2nd part duodenum	1	0
4	71	Female	DM, HT, DLP	Distal cholangiocarcinoma	1st-2nd part duodenum	0.5	0
5	47	Female	None	Breast cancer with pancreatic metastasis	1st-2nd part duodenum	2	0
6	51	Female	None	Right-sided colon cancer	Pylorus to 2nd part duodenum	0.5	0
7	59	Female	None	Gallbladder cancer	1st-2nd part duodenum	3	0
8	62	Male	None	Carcinoma of the head of pancreas	2nd-3rd part duodenum	3	1
9	71	Female	None	Carcinoma of the head of pancreas	2nd part duodenum	2	0
10	58	Female	None	Carcinoma of the uncinate process of the pancreas	1st-2nd part duodenum	3	1
11	35	Female	DM, neurogenic bladder, acute kidney injury, urinary tract infection	SMA syndrome	2nd -3rd part duodenum	6	1
12	82	Female	HT, CKD, DLP, Compression fracture T11	Duodenal obstruction unidentified cause	2nd part duodenum	1	0

Abbreviations: GOO: gastric outlet obstruction, CHF: congestive heart failure, DM: diabetes mellitus, HT: hypertension, DLP: dyslipidemia, CKD: chronic kidney disease

TABLE 3. Patient and procedural characteristic

Patient	Techniques	Stent size (mm)	Technical success	Adverse events	LOS (day)	Post-op. GOO score	Clinical success	Recurr.	F/U (Mo.)
1	Direct over-the-guidewire	10x15	No	misdeployment & Peritonitis	10	-	-	-	-
2	Wireless-freehand	10x20	Yes	No	8	3	Yes	Yes	22
3	Wireless-freehand	10x20	Yes	No	19	3	Yes	No	20
4	M-EPASS	10x15	Yes	No	12	3	Yes	No	7
5	M-EPASS	10x20	Yes	No	8	2	Yes	No	5
6	Missing data	10x20	Yes	No	18	3	Yes	No	1
7	Wireless-freehand	10x20	Yes	No	13	3	Yes	No	4
8	M-EPASS	10x20	Yes	No	29	3	Yes	No	1
9	Wireless-freehand	10x20	No	misdeployment	11	3	Yes	No	4
10	M-EPASS	10x20	Yes	No	12	3	Yes	No	0.75
11	M-EPASS	10x20	Yes	No	72	2	Yes	No	5
12	M-EPASS	10x20	Yes	No	9	3	Yes	No	2

Abbreviations: LOS: length of hospital stay, Post-op: postoperative, GOO: Gastric outlet obstruction, Recurr: recurrent, F/U: follow up, M-EPASS: Modified endoscopic ultrasound-guided double-balloon occluded gastroenterostomy bypass

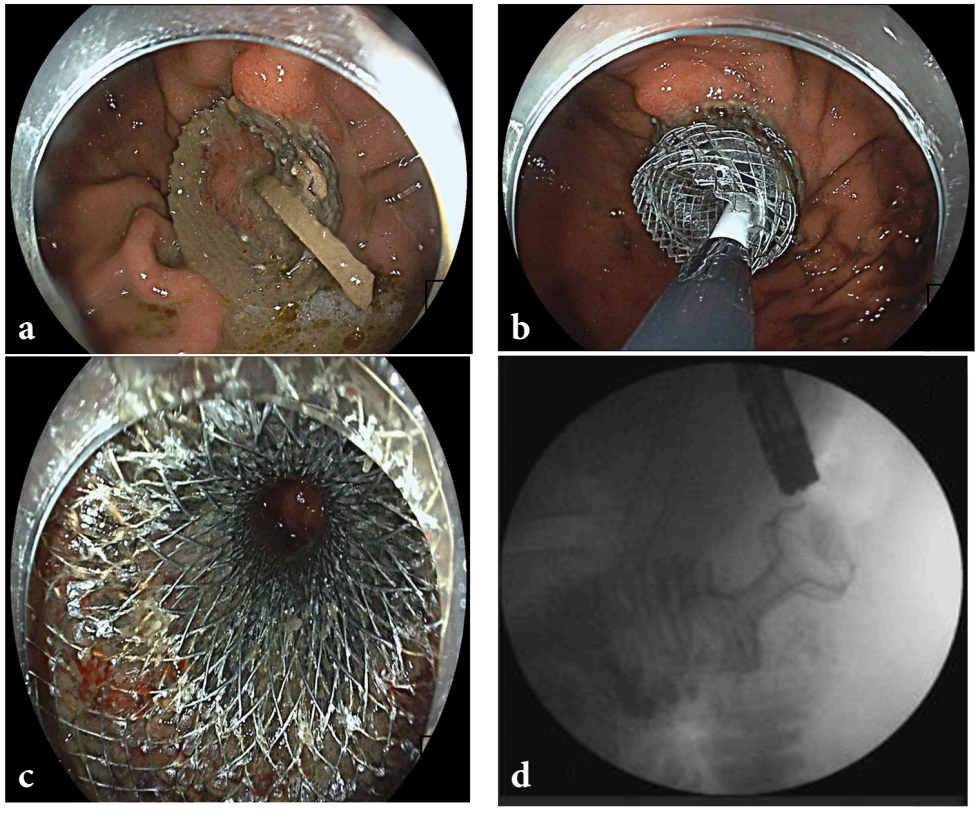

Fig 3. a. Previous stent occlusion, b. Deploying the second stent (stent in stent technique) using a therapeutic gastroscope, c. Endoscopic image showing patency of the stent after deploying the second stent, d. Contrast study showing good patency of the stent.

DISCUSSION

Surgical gastrojejunostomy, both open and laparoscopic, was a modality of treatment for malignant GOO which had long-term patency but entailed high morbidities because of patients being unfit for surgery. Endoscopic duodenal stenting replaced it as a minimally invasive treatment which yielded benefits in terms of rapid relief of obstructive symptoms and shorter hospital stay, but this modality resulted in high rates of recurrent obstruction due to tumor ingrowth with the need for reintervention, and it was therefore proposed for the treatment of choice only in cases with a life expectancy of shorter than 3 months.[2] EUS-GE has recently become the preferred alternative treatment with many multicenter studies, reviews, systematic reviews and meta-analyses demonstrating that it was minimally invasive, had rapid efficacy and longer patency than endoscopic duodenal stenting, and had similar patency but fewer adverse events compared to surgery.[2-5]

Earlier designs of the deployment system of LAMS had no cautery tip, so that the EUS-GE procedure involved multiple steps, such as transmural puncture, placement of a guidewire, and needle tract dilation using a balloon or cautery dilator catheter followed by LAMS with over-the-guidewire deployment. The complexity of the procedure affected technical success as well as adverse events, with earlier publications reporting technical success ranging from 90-92 %[6,7]; however, some patients required salvage procedures, such as bridging, using fully-covered self-expandable metal stents (FCSEMS) or utilizing LAMS via the natural orifice transluminal endoscopic surgery (NOTES) technique, to correct the misplaced stents. One study also reported major adverse events (11.5%) from peritonitis, bleeding and abdominal pain resulting in the need for laparotomy.[7]

Recently, an electrocautery-enhanced LAMS has been developed and is widely used for EUS-GE in order to allow multi-step stent placement in a single device which decreases operative time and appears to increase technical success and minimize adverse events. On W. et al[8] reported EUS-GE using cautery-enhanced LAMS in a multi-center study. Various techniques were used and demonstrated a technical success rate of 92% with just 8% of moderate adverse events resulting from mis-deployment. With this in mind, our center favored the use of the electrocautery-enhanced LAMS to simplify the technical steps, and we achieved similar overall technical success of 83.3% (range 75-100% for each technique) with just one (8.3%) severe adverse event.

One major concern in performing EUS-GE regards the need for improvement of the method used for stent deployment in order to improve technical success and minimize complications. The technique has been developed through various clinical trials and can be classified into 2 types: the direct over-the-guidewire technique and the wireless-freehand insertion method.[9-11]

The direct over-the-guidewire method, with or without pre-procedural saline infusion into the small bowel loop, requires a trans-gastric puncture using a 19-gauge needle to enable preloading of a guidewire into the targeted loop and a one-step exchange to the electrocautery-enhanced LAMS system before the stent is deployed. Physicians in some clinical trials have preferred using a balloon-assisted (targeted) method involving preloading a 15-20 mm. stone-retrieval balloon or balloon dilation catheter over the guidewire into the targeted enteral loop before making a trans-gastric puncture of the inflated balloon to help confirm that the correct enteral loop has been punctured before continuing with the next step of deploying the LAMS. Chen YI et al.[12] reported that these two techniques seem to be comparable in terms of technical success and safety[12] The disadvantage of the over-the-guidewire technique is that it requires more exchanges and carries a risk of mis-deployment as a result of rapid fluid migration from the target loop[10], which can push the stent during the procedure.[11]

The wireless-freehand insertion technique requires some devices to assist with fluid administration into the target intestinal loop to achieve good visualization under EUS. Placing an oroenteral catheter used to be the most popular technique, as it was easy to find suitable catheters. Insertion of a specially designed double-balloon enteric tube (Tokyo Medical University type; Create Medic Co., Ltd, Yokohama, Japan), called an endoscopic ultrasonography-guided double balloon-occluded gastrojejunostomy bypass (EPASS), across the obstruction point was another option. The additional procedure prior to insertion of the LAMS system involved inflating the two balloons with contrast medium and infusing fluid into the small bowel segment between the two balloons to facilitate stent placement. However, these specially designed catheters are not commercially available worldwide. Lately, many studies' authors have advocated the use of the wireless-freehand insertion technique, as they believe it to be superior to the direct over-the-guidewire method in terms of safety and efficacy because of its high technical success of 98-100% and its low incidence of adverse events (2.8-7%) without severe complications[13-15]; on the other hand, others have claimed that the EPASS procedure potentially enhances technical success and safety.[16,17] Basha J, et al.[18] reported that EUS-GE with the EPASS technique was also feasible

in patients presenting with ascites, stating technical success of 91.6%, clinical success of 83.3 and 0% adverse events, and these results were not significantly different from those achieved in patient without ascites.

Mario A, et al.[19] developed a technique to mimic EPASS by using two vascular balloons, which they called a modified approach to EUS-guided double-balloon-occluded gastroenterostomy (M-EPASS), to facilitate EUS-GE. The technical success rate was 91%, clinical success was 80%, and there was just one adverse event due to stent migration. The M-EPASS technique seems to be comparable with EPASS, but the latter has the advantage of using commercially available accessories.

Over 20 single-arm studies have been published about EUS-GE in malignant GOO, with technical success varying between 80-100%, clinical success 73-95% and serious adverse events numbering approximately 3-6%.[20] The results achieved in our center seem comparable with overall technical success. The M-EPASS technique and the wireless freehand combined with oroenteral catheter were 83.3%, 100% and 75% respectively. One incidence (8.3%) of a severe adverse event from the direct over-the-guidewire technique persuaded us to change our technique of preference to the wireless-freehand method, and we are now becoming more comfortable with the M-EPASS technique. The high incidence of mis-deployment of 16.7% (2/12) is probably related to the learning curve associated with becoming familiar with the procedure, as proficiency is normally achieved after completion of 7-25 procedures.[20]

With regard to clinical success associations with stent size and patency, recent studies have recommended that a large luminal diameter with the 20-mm LAMS is technically feasible and more likely to achieve tolerance of a soft solid or complete diet.[15,20-21] This recommendation is in keeping with the findings of our study, in which the majority of stents used for EUS-GE were 20-mm, and the patients still had GOO score of 2-3 in the mean follow up period of 6.2 months (range 0.75-22 months), with longest patency of about 20 months and one stent occlusion from tissue ingrowth at 12-month follow up. Only two patients received 15-mm stent: one of these had technical failure due to mis-deployment, while the other still had good GOO score at 7-month follow up.

Some retrospective studies have reported the use of EUS-GE specifically for benign conditions, such as peptic stricture, anastomotic stricture, duodenal hematoma, acute/chronic pancreatitis, pancreatic pseudocyst/walled-off pancreatic necrosis, superior mesenteric artery syndrome, and caustic stricture[22,23] They demonstrated that it was a promising modality for benign GOO, especially for cases which were unlikely to respond to dilation therapy or in cases when this technique was not possible. Physicians were able to avoid surgery for GOO in 83.3% of cases.[23] The technical and clinical success rates were similar to those of patients with malignant conditions. The most commonly reported adverse events occurred mostly in mild conditions such as abdominal discomfort and stent mis-deployment, but there were also some severe adverse events. Chen YI et al.[22] reported gastric leak after elective stent removal which needed surgical intervention, and James TW et al.[23] reported bleeding from a gastric ulcer at the anastomotic site 2 days after the procedure. There was also a case of small bowel obstruction resulting from LAMS migration 1 year after deployment which required laparotomy for removal of the stent, while in another patient, the gastrojejunostomy stent was found to have transversed from the stomach through the colon and into the jejunum but without contrast leakage. Recurrence of GOO while the stent was in place was mostly caused by food impaction, and this was successfully managed by endoscopic removal, but there were some cases which needed surgical intervention.[22,23] James TW et al.[23] recommended that the stent stay in place for a mean time of 8.5 months and should be removed after improvement in GOO to avoid complications from the stent; however, some recurrent GOO still occurred after stent removal. Our study showed one good response after EUS-GE in a benign condition (SMA syndrome), with the patient having the stent removed at 5-month follow up. Generally in case of malignant, LAMS will be reintervention when re-obstructive symptoms occur. In case of benign condition apart from re-obstruction, Elective exchange should be considered to avoid troublesome of tissue ingrowth and overgrowth. Six month interval is preferable by expert endosonographers.[24]

CONCLUSION

EUS-GE is effective in the management of GOO, and the wireless freehand method combined with the M-EPASS technique or oroenteral catheter should be the technique of choice in term of safety and efficacy. However, a larger prospective study is needed to further evaluate this technique in treating both benign and malignant GOO.

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Fecal Calprotectin in Nosocomial Diarrhea: A Prospective Observational Study

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ABSTRACT

Objective: Fecal calprotectin (FC) has an essential role in differentiating inflammatory diarrhea from functional diarrhea in an outpatient setting; however, its role in nosocomial diarrhea remains not well explored.

Materials and Methods: This is a prospective observational study. We included adult inpatients with nosocomial diarrhea and categorized them into diarrhea likely (group A) and unlikely (group B) to have lesions in the colonic mucosa. Group A included infectious diarrhea such as *Clostridium difficile* and ischemic colitis. Group B comprised tube-feeding diarrhea, non-*C. difficile* antibiotic-associated diarrhea, and drug-induced diarrhea. The FC levels were compared between the two groups.

Results: 135 patients were included, 45 in group A and 90 in group B. Median FC was 902 mg/kg (interquartile range [IQR] 549-2,175) of feces in group A, significantly higher than the median level of 377 mg/kg (IQR 141-664) of feces in group B (p<0.001). The area under the receiver operating characteristic curve was 0.798 (95% confidence interval: 0.717-0.879). At the standard cutoff of 50 mg/kg of feces, the sensitivity and specificity were 97.8% and 7.8%, respectively.

Conclusion: FC was significantly higher in nosocomial diarrhea likely to have mucosal lesions; however, its clinical usefulness was limited due to poor specificity.

Trial registration: The trial was registered at ClinicalTrials.gov. (reg. no. NCT04491799. Registered on 26/04/2020).

Keywords: Nosocomial diarrhea; fecal calprotectin; *Clostridium difficile* (Siriraj Med J 2024; 76: 182-188)

INTRODUCTION

Nosocomial diarrhea is defined as diarrhea that develops after 72 hours of hospitalization.[1] It is a commonly occurring condition with a reported prevalence of 14-21% in patients in the intensive care unit.[2] Common causes of nosocomial diarrhea can be grouped into two main groups according to the mucosal abnormality.[3] The first group includes conditions with gastrointestinal (GI) mucosal lesions, which mainly comprises gastrointestinal infections, including *Clostridium difficile* infection (CDI) and other infections such as cytomegalovirus infection, and some other conditions such as ischemic colitis. The second group includes conditions with normal colonic mucosa, including antibiotic-associated diarrhea (AAD) without CDI, tube-feeding-associated diarrhea, and drug-induced diarrhea.[2,3] The current management recommendations include ruling out infections, particularly *C. difficile* infection, which is found in a majority of cases. Afterward, diet modification and supportive treatment with anti-diarrheal agents are recommended.[4] However, some patients have ongoing diarrhea despite receiving appropriate management, which could be

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due to undetected *C. difficile*, unresolved tube-feeding diarrhea/AAD, or other causes such as reactivation of cytomegalovirus infection and ischemic enterocolitis. Colonoscopy may be required in this setting to establish a definite diagnosis. Nonetheless, colonoscopy is invasive and has some complications, particularly in patients with a critical illness. Therefore, selecting patients who are likely to have mucosal lesions and gain benefit from colonoscopy is warranted. A test to differentiate diarrhea with and without mucosal lesions should be helpful in this situation. Unfortunately, a conventional test like stool white blood cell (WBC) has a low sensitivity in detecting mucosal lesions in an inpatient setting.[3]

Fecal calprotectin is an easy, non-invasive test that can differentiate inflammatory bowel disease and other functional disorders in an outpatient setting.[5] However, the data in an inpatient setting is limited to the studies focusing on diagnosis and assessment of the severity of *C. difficile*-associated colitis.[6-11] Our main objective was to study the performance of fecal calprotectin for distinguishing patients with nosocomial diarrhea likely to have mucosal lesions from those unlikely to have mucosal lesions.

MATERIALS AND METHODS

Study design

This study is a prospective observational study conducted from February 2019 to May 2020. The protocol was approved by Siriraj Institutional Review Board, an independent ethics committee according to local requirements, and informed consent was obtained from all participants before study enrollment. The trial was registered at ClinicalTrials.gov. (reg. no. NCT04491799).

Participants and recruitment process

Adult patients aged at least 18 years who developed nosocomial diarrhea were eligible for inclusion. The definition of nosocomial diarrhea was a development of loose stool or watery stool (Bristol Stool Form type 6-7) at least three times per day after hospitalization for longer than 72 hours. The patients with known underlying GI inflammatory conditions such as inflammatory bowel disease were excluded. The stool samples were collected and stored at -20 at enrollment. Afterward, study patients were managed by treating physicians. All study patients were followed up until death or discharge from the hospital. The stool samples were tested for calprotectin at the end of the study. Therefore, treating physicians did not know the fecal calprotectin values.

Eligible patients were required to have stool microscopic examination and stool test for *C. difficile* infection. Stool ova & parasite and stool culture were sent in some patients with clinical suspicion. Colonoscopy was performed in some patients when the stool tests could not make the diagnosis, and the clinical did not improve by the conservative management, depending on the treating physician's decision.

The clinical data, investigations, final diagnoses, and clinical outcomes were prospectively collected. The definitions of each diagnosis are shown as follows:

- *Clostridium difficile* infection: positive stool *C. difficile* toxin. The test was performed on a BD MAX System detecting *C. difficile* toxin B gene (tcdB) by real-time polymerase chain reaction (PCR) technique.
- Presumed *Clostridium difficile* infection: the presence of stool WBC more than 5/high power field, but negative for *C. difficile* toxin with clinical response to *C. difficile* treatment in one week
- Cytomegalovirus infection: histopathological identification of viral inclusion body or positive immunohistochemistry
- Bacterial enterocolitis: stool culture growth of bacterial pathogen
- *Strongyloides stercoralis* infection: detected larvae of *Strongyloides stercoralis* in stool examination
- Ischemic colitis: endoscopic findings and pathological findings suggestive of colonic ischemia
- Tube-feeding-associated diarrhea: no WBC or organisms were detected in stool, and diarrhea responded to diet modification, such as decreased concentration or rate, or changed the type of enteral diet
- Antibiotic-associated diarrhea (AAD): no WBC or organisms were detected in stool, and diarrhea responded to stopping or changing antibiotics with or without cholestyramine
- Drug-induced diarrhea: no WBC or organisms were detected in stool. Diarrhea occurred within 48 hours after taking potential drugs, such as elixir KCL or laxative agents, and responded to discontinuation of those medications.

Treatment response was defined as a reduction in the frequency of bowel movements to less than three times per day. If a definite diagnosis could not be made, those patients were excluded from the study.

Study participants were divided into the group likely to have mucosal lesions (group A) and those likely to have normal colonic mucosa (group B). Group A included patients with diarrhea associated with gastrointestinal infections, including *C. difficile*, other bacteria, cytomegalovirus, strongyloidiasis, and other conditions, such as ischemic

colitis. Group B included the patients with tube-feeding diarrhea, AAD, and drug-induced diarrhea.

Fecal calprotectin measurement

The stool samples were extracted at room temperature using an EliA Stool Extraction Kit. Fecal calprotectin levels were measured by EliA Calprotectin Test Kit on a Phadia 100 analyzer based on the principle of a two-site sandwich fluoroenzyme immunoassay. The results were reported in mg/kg of feces with a measurement range of 15 to ≥3,000 mg/kg of feces. A fecal calprotectin level higher than 3,000 mg/kg of feces was defaulted to 3,000 mg/kg for analysis in this study.

Study outcomes

The primary outcome was the fecal calprotectin performance in distinguishing nosocomial diarrhea likely to have mucosal lesions from those unlikely to have mucosal lesions.

Statistical analysis

The continuous data are presented as mean and standard deviation if normally distributed and as median and range or interquartile range (IQR) if not normally distributed. Categorical variables are presented as frequency and percentage. Comparison of factors and patient characteristics between group A and group B were undertaken using an independent *t*-test or Wilcoxon rank-sum test for continuous variables and using the chi-square test or Fisher's exact test for categorical variables. The best fecal calprotectin level cutoff for distinguishing between groups A and B was determined using receiver operating characteristic (ROC) curve analysis. The performance of different cutoff values in the diagnosis of diarrhea likely to have mucosal lesions was determined using the following parameters: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratio (LR). A p-value < 0.05 was considered statistically significant. The statistical analyses were performed using SAS Statistics software (SAS, Inc., Cary, North Carolina, USA) and R program version 4.0.1(R Foundation for Statistical Computing, Vienna, Austria). The OptimalCutpoints[12] software packages were used.

RESULTS

Baseline characteristics

One hundred and forty-two patients were assessed. Seven were excluded because a definite diagnosis could not be established. The remaining 135 patients were analyzed in this study.

Baseline characteristics are shown in Table 1. The mean age was 74 years, and 41% were male. About 80% of patients had comorbid illnesses, such as atherosclerotic diseases, chronic kidney diseases, chronic liver diseases, autoimmune diseases, and malignancies. The most common indication for hospitalization was a severe infection.

At the time of stool collection, 46% were on a mechanical ventilator, 36% required inotropic agents, and 8% needed acute hemodialysis. Seventy-six percent of patients required tube-feeding enteral nutrition with a median rate of 600 cc/hour (range: 10-600). Ninety-eight percent of subjects were receiving antibiotics with a median duration of 4.5 days (range:0-26) before diarrhea developed.

Diarrhea developed at a median duration of 7 days of hospitalization. Four (3.0%) and 14 (10.4%) patients had bloody and mucous diarrhea, respectively. The mean maximum number of bowel movements per day and volume of stool per day were 6.4 times and 732 ml, respectively. Abdominal pain, fever, and feeding intolerance were found in 8.9%, 60.7%, and 9.6%, respectively. The mean hemoglobin and albumin levels were 9.50 g/dL and 2.66 g/dL, respectively.

The definite diagnoses of study patients are shown in Table 2. Forty-five patients (33.3%) were in group A; the diagnoses included CDI, GI-CMV disease, bacterial enterocolitis, *Strongyloides stercoralis*, and ischemic colitis. Ninety patients (66.7%) were in group B.

The patients in group A were significantly younger. Passing bloody and mucous stools, abdominal pain, and feeding intolerance was found more in group A while tube-feeding nutrition was required more in group B. Stool WBC was found in only 11 (24.4%) patients in group A. Other parameters were not statistically different between groups.

Fecal calprotectin in diagnosis of nosocomial diarrhea

The level of fecal calprotectin in group A was significantly higher than the level in group B, with a median level of 902 mg/kg (interquartile range [IQR]: 549-2,175) and 377 mg/kg (IQR: 141-664), respectively (p<0.001) (Fig 1A). Using fecal calprotectin level for diagnosis of diarrhea likely to have mucosal lesions generated an area under the ROC curve of 0.798 (95% confidence interval [CI]: 0.717-0.879) (Fig 1B). The sensitivity, specificity, PPV, NPV, positive LR, and negative LR of the cutoff values of 50 mg/kg of feces, which was recommended by the American Gastroenterology Association[13], and 708 mg/kg, which was the best cutoff value for this cohort, are shown in Table 3.

TABLE 1. Clinical and laboratory parameters of total cohort and comparison between diarrhea likely to have mucosal lesions (Group A) and unlikely to have mucosal lesions (Group B)

	Total cohort (n=135)	Group A (n=45)	Group B (n=90)	*p*-value
Demographic data				
Age	74.2 ± 14.0	69.3 ± 16.1	76.6 ± 12.3	0.010
Male	55 (40.7%)	21 (46.7%)	34 (37.8%)	0.322
Significant comorbid illness	109 (80.7%)	39 (86.7%)	70 (77.8%)	0.217
Hospitalizations				
Indication for hospitalization				0.126
Infections	98 (72.6%)	28 (62.2%)	70 (77.8%)	
Cancers	7 (5.2%)	4 (8.9%)	3 (3.3%)	
Major organ diseases	30 (22.2%)	13 (28.9%)	17 (18.9%)	
In hospital setting				
On ventilator	62 (45.9%)	16 (35.6%)	46 (51.1%)	0.087
On inotropic agents	48 (35.6%)	15 (33.3%)	33 (36.7%)	0.703
Need acute hemodialysis	11 (8.2%)	3 (6.7%)	8 (8.9%)	0.751
Sepsis	61 (45.2%)	22 (48.9%)	39 (43.3%)	0.541
Enteral nutrition and antibiotics				
Tube feeding enteral nutrition	102 (75.6%)	23 (51.1%)	79 (87.8%)	<0.001
Antibiotics	132 (97.8%)	43 (95.6%)	89 (98.9%)	0.258
Duration of antibiotics (median, range)	4.5 (0 – 26)	4 (0 – 18)	5 (0 – 26)	0.382
Clinical manifestations				
Day after admission (median, range)	7.0 (3 – 95)	6 (3 – 95)	7 (3 – 45)	0.434
Diarrhea character				
Watery	135 (100%)	45 (100%)	90 (100%)	
Bloody	4 (3.0%)	4 (8.9%)	0 (0.0%)	0.011
Mucous	14 (10.4%)	11 (24.4%)	3 (3.3%)	<0.001
Maximum bowel movement/day	6.4 ± 2.3	6.73 ± 3.16	6.18 ± 1.69	0.284
Maximum volume/day	732 ± 423	696 ± 443	750 ± 414	0.525
Abdominal pain	12 (8.9%)	8 (17.8%)	4 (4.4%)	0.020
Fever	82 (60.7%)	27 (60.0%)	55 (61.1%)	0.900
Feeding intolerance	13 (9.6%)	9 (20.0%)	4 (4.4%)	0.010
Laboratory tests				
Hemoglobin (g/dL)	9.50 ± 1.64	9.4 ± 1.9	9.6 ± 1.5	0.590
White blood cell count (per mm^3)	11161 ± 5764	11677 ± 6462	10903 ± 5402	0.464
Platelet count (per mm^6)	230 ± 125	220 ±143	236 ±117	0.524
Creatinine (mg/dL) (median, range)	1.13 (0.27–11.26)	1.26 (0.32–11.18)	1.08 (0.27 – 11.26)	0.448
Bicarbonate (mEq/L)	22.9 ± 4.9	22.0 ± 4.3	23.4 ± 5.1	0.114
Albumin (g/dL)	2.66 ± 0.53	2.66 ± 0.56	2.66 ± 0.52	0.956
Presence of stool white blood cell	11 (8.2%)	11 (24.4%)	0 (0%)	<0.001
Outcome				
Died	38 (28.2%)	16 (35.6%)	22 (24.4%)	0.176

TABLE 2. Final diagnoses of patients in this cohort

Definite diagnosis	
Clostridium difficile infection	32 (23.7%)
Presumed *C.difficile* infection	5 (3.7%)
Gastrointestinal cytomegalovirus disease	3 (2.2%)
Bacterial enterocolitis	2 (1.5%)
Strongyloides stercoralis	2 (1.5%)
Ischemic colitis	1 (0.7%)
Tube-feeding diarrhea	41 (30.4%)
Drug-induced diarrhea	15 (11.1%)
Antibiotic-associated diarrhea	34 (25.2%)

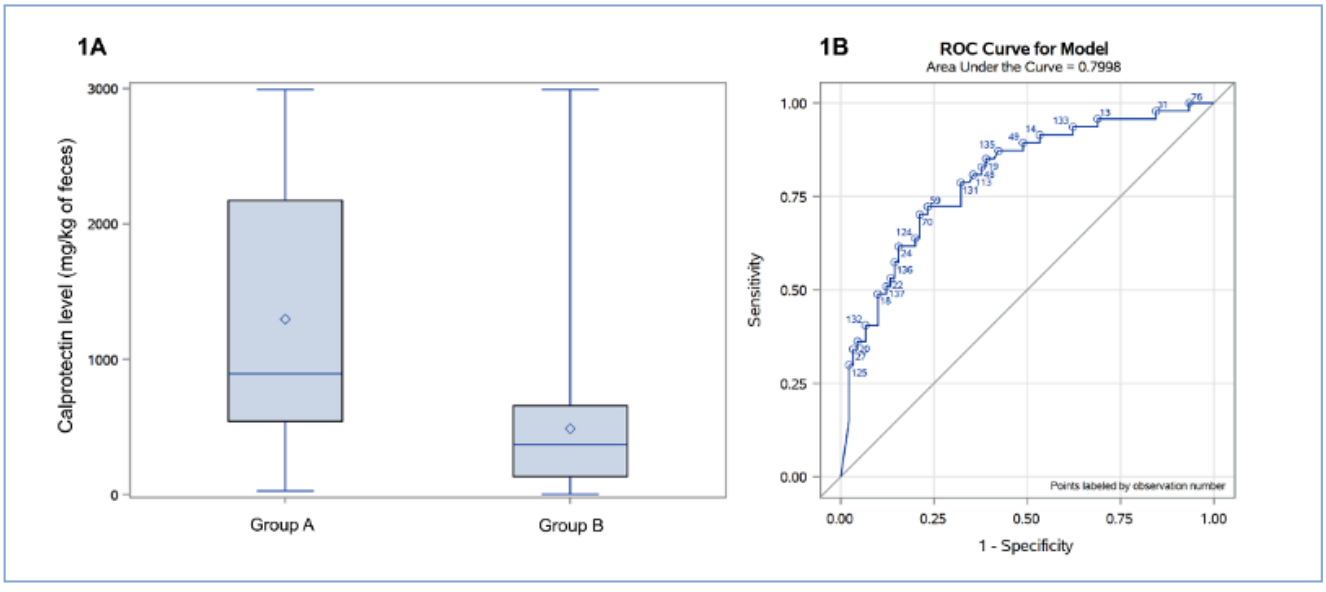

Fig 1. The box plot showed fecal calprotectin levels in groups A and B (Fig 1A). The bottom and top of each box represent the 25th and 75th percentiles, giving the interquartile range. The blue line within the box indicates the median, the diamond-shaped figure within the box indicates the mean, and the error bars indicate the 10th and 90th percentiles. Fig 1B shows the receiver operating characteristic (ROC) curve of fecal calprotectin levels for differentiating groups A from B.

TABLE 3. Calprotectin levels in the diagnosis of diarrhea likely to have mucosal lesions

Cutoff (milligrams per kilograms feces)	Sensitivity	Specificity	PPV	NPV	Positive LR	Negative LR
50 (standard cutoff value)	98%	8%	35%	87%	1.06	0.28
708 (best cutoff value)	71%	79%	63%	84%	3.37	0.37

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ration

At the standard cutoff value of 50 mg/kg of feces, the sensitivity, specificity, and accuracy were 97.8%, 7.8%, and 37.8%, respectively. At this cutoff value, 1 of 45 (2.2%) patients in group A would have been misdiagnosed with diarrhea unlikely to have mucosal lesions, and 83 of 90 (92.2%) patients in group B would have been misdiagnosed with diarrhea likely to have mucosal lesions.

At the cutoff value of 708 mg/kg of feces, the sensitivity, specificity, and accuracy were 71.1%, 78.9%, and 76.3%, respectively; 13 of 45 (28.9%) patients in group A and 19 of 90 (21.1%) patients in group B would have been misdiagnosed.

DISCUSSION

Fecal calprotectin is a marker used to differentiate inflammatory bowel disease from irritable bowel syndrome in an outpatient setting. However, its benefit in an inpatient setting has not been well studied. This study showed that in this cohort, which comprised mainly the elderly and more than half in an ICU setting, fecal calprotectin was significantly higher in patients with GI infections and ischemic colitis than in patients with diarrhea unlikely to have mucosal lesions; however, the clinical usefulness was limited owing to its poor specificity.

This performance of fecal calprotectin in differentiating nosocomial diarrhea likely and unlikely to have mucosal lesions in this study is consistent with previous studies that compared fecal calprotectin levels between patients with CDI and those with other causes of nosocomial diarrhea.[7-9,14,15] The area under the ROC curve was comparable between our study (0.798) and other studies (0.82-0.86)[7,9,14], while Barbut *et al.* reported a lower area under the ROC curve of 0.62.[8] Interestingly, all studies, including this study, showed considerably overlapping fecal calprotectin levels between the group with and without mucosal lesions, which resulted in only fair test performance, in contrast to its good performance in an outpatient setting. However, the reported fecal calprotectin levels varied in our study and previous studies, particularly those without mucosal inflammation. The median level of fecal calprotectin in our study group with mucosal lesions was 902 mg/kg of feces, whereas the median level ranged from 183-983 mg/kg of feces in patients with CDI in other studies.[7-9,14,15] The median level in the group unlikely to have mucosal lesion was 377 mg/kg of feces in our study, while they ranged from <100 to 145 mg/kg of feces in the control groups in other studies.[7-9,14,15] This variation may be attributed to differences in patient characteristics between and among cohorts. Our cohort had more than half of the patients in an ICU setting, 75% with tube-feeding nutrition, and almost all patients were receiving antibiotics – all of which could cause mesenteric blood flow disturbance and bacterial dysbiosis, which could result in some degree of microscopic inflammation.[16] Although the fecal calprotectin level differed among studies, many cohorts, including this cohort) reported that the control group's fecal calprotectin level was elevated when using the cutoff used in outpatient settings.[8,14,15]

Despite the significant difference in fecal calprotectin levels in patients likely and unlikely to have mucosal lesions, this study suggested that fecal calprotectin should not be used in a nosocomial setting. As high as 92% of patients in the group unlikely to have mucosal lesions had the fecal calprotectin level above the standard cutoff value of 50 mg/kg of feces and might have had undergone unnecessary colonoscopy if management decision had been made based on the level of fecal calprotectin. Barnes *et al.* reported that fecal calprotectin levels rarely changed inpatient management and had no significant difference in the usage of subsequent diagnostic colonoscopy.[17]

The strength of this study is that our data were prospectively collected. Moreover, there was no bias in data collection because fecal calprotectin level was not measured until the end of the study after all clinical data had been collected. This study has some limitations. First, the method to diagnose CDI was a PCR-based technique that could detect both colonization and infection.[18] This could explain the low calprotectin levels in some patients with positive *C. difficile* tests. Second, this study has a relatively small sample size of patients who required a colonoscopy to obtain a definite diagnosis.

In conclusion, fecal calprotectin had suboptimal performance in nosocomial diarrhea compared to the outpatient setting due to significant overlapping levels between the patient likely and unlikely to have mucosal lesions.

List of abbreviations

AAD	antibiotic-associated diarrhea
CDI	*Clostridium difficile* infection
GI	gastrointestinal
IQR	interquartile range
LR	likelihood ratio
NPV	negative predictive value
PPV	positive predictive value
ROC	receiver operating characteristic
WBC	white blood cell

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the policy of author's institute but are available from the corresponding author on reasonable request.

Competing interests

All authors declare no personal or professional conflicts of interest relating to any aspect of this study.

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The Role of Lactate-based Serum Tests for Prediction of 30-day Mortality in Hospitalized Cirrhotic Patients with Acute Decompensation: A Prospective Cohort Study

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ABSTRACT

Objective: Cirrhotic patients with acute decompensation are associated with high short-term mortality. The prognostic performance of venous lactate (VLAC) for mortality prediction in these patients has not been well established. This study aimed to evaluate the role of several lactate-based serum tests for prediction of 30-day mortality in these patients.

Materials and Methods: Cirrhotic patients with acute decompensation were prospectively enrolled. VLAC on admission and at 6, 12, and 24 hours were determined. Lactate clearance (LAC-Cl), MELD-lactate, and MELD-lactate clearance (MELD-ΔLA) at each timepoint were calculated and compared between 30-days survivors and non-survivors.

Results: 74 patients were included (age 69±13 years, 66.2% male, MELD 18.3±7). The main indications for admission were infection (67.6%) and gastrointestinal bleeding (18.9%). The 30-day mortality rate was 29.7%. Initial VLAC was significantly higher in non-survivors (9.7±8 vs. 3.61±1.79 mmol/L, P<0.001). In addition, VLAC at 6, 12, 24 hours, MELD-Lactate and MELD-ΔLA scores were significantly higher in non-survivors. Based on ROC analysis, the VLAC, MELD-Lactate, and MELD-ΔLA at 6 hours were reliable predictors of 30-day mortality (AUROC 0.79, 0.86, and 0.86, respectively). However, compared to MELD score (AUROC 0.81), no significant difference was found.

Conclusion: In hospitalized cirrhotic patient with acute decompensation, VLAC, MELD-Lactate and MELD-ΔLA at 6 hours are simple, and reliable predictors for 30-day mortality.

Keywords: Cirrhosis; lactate; liver decompensation (Siriraj Med J 2024; 76: 189-197)

INTRODUCTION

Liver cirrhosis is the final pathway of various chronic liver diseases, and responsible for significant morbidity and mortality. Acute decompensation, which is characterized by worsening ascites, infection, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome, and/or jaundice, is the most common indication for hospitalization among these patients. The economic burden of cirrhosis is also increasing, particularly with hospitalized decompensated cirrhosis, as evidenced by increased hospital admissions, longer lengths of stay, and high mortality rates.[1,2] Therefore, it is crucial to develop a scoring system that can early identify patients with a high mortality risk, allowing for timely intervention to improve outcomes in this population.

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Currently, Child-Pugh and Model for End-Stage Liver Disease (MELD) scores are the most commonly used tool for prognostication in patients with cirrhosis. Child-Pugh score is easily determined, although some variables depend on individual judgment. In addition, MELD score is not based on subjective evaluation but rather on computation.[3] Venous lactate level (VLAC) is an indicator of tissue hypoxia or a decrease in the excretory function of lactate.[4,5] Patients with cirrhosis have decreased hepatic gluconeogenesis and increased glycolysis, resulting in a net increase in lactate level[6] VLAC and Lactate Clearance (LAC-Cl) have been proposed as basic predictors of disease severity, prognosis, and mortality. In addition, it can be used as a potential resuscitation marker.[4] Previous study has shown that serum lactate levels accurately represent disease severity, organ failure, and is related with short-term mortality in critically ill patients with liver cirrhosis.[7] However, information in the role of VLAC and other lactate-based tests (LAC-Cl, MELD-lactate, and MELD-lactate clearance) for prognostic prediction in hospitalized cirrhotic patients with acute decompensation is limited. This study was aimed to explore the role of various lactate-based serum tests for prediction of 30-day mortality in these patients.

MATERIALS AND METHODS

Study design

This prospective cohort study was conducted at the Internal Medicine ward of Thammasat University Hospital in Pathumthani, Thailand, from April 2020 to March 2021. This study enrolled hospitalized cirrhotic patients with acute decompensation, aged between 18 and 80 years old. Diagnosis of cirrhosis was established through a combination of clinical, laboratory, and radiographic assessments, supplemented by histological evidence where available. Acute decompensation was defined by the presence of at least one of the following indicators: upper gastrointestinal bleeding, bacterial infection, worsening or uncontrolled ascites, acute kidney injury, or hepatic encephalopathy.

Exclusion criteria included severe heart diseases defined as New York Heart Association class III or IV or severe pulmonary diseases, end stage kidney disease requiring hemodialysis, human immunodeficiency virus infection, pregnancy, time between admission and evaluation for inclusion >24 hours, and refusal to participate in the study. All patients received standard treatment in accordance with established guidelines for managing acute decompensated cirrhosis. This study received ethical approval by the Human Research Ethics Committee of Thammasat University, Thailand, and was conducted according to the good clinical practice guideline, as well as the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study protocol and data collection

Demographic information, cirrhosis etiologies, medical histories, and physical examination findings were recorded. Laboratory assessments, including complete blood counts, comprehensive metabolic panels, hemocultures, ascitic fluid analyses and cultures (where applicable), urinalyses, and urine cultures were conducted. Additionally, the severity of liver impairment was evaluated using the Child-Pugh score and Model for End-Stage Liver Disease (MELD) score.

Over the course of 24 hours following admission, measurements of venous lactate (VLAC) were obtained at intervals of 0, 6, 12, and 24 hours (Calorimetric Method). The LAC-Cl (lactate clearance) was determined by the formula: LAC-Cl (%) = (initial VLAC - subsequent VLAC) / initial VLAC x 100. Furthermore, the MELD-Lactate score was computed using the formula: 5.68 × loge (lactate) + 0.64 × (Original MELD) + 2.68. The MELD-ΔLA (MELD-Lactate clearance) was calculated based on creatinine levels (mg/dL), bilirubin levels (mg/dL), INR, admission lactate levels (mmol/L), LAC-Cl (%), and history of vasopressor usage, as elaborated elsewhere.[8] MELD- ΔLA was calculated based on LAC-Cl at 6, 12, and 24 hours.

Study outcome

Primary outcome of this study was to evaluate the efficacy of various lactate-based serum tests (VLAC, LAC-Cl, MELD-Lactate, and MELD-ΔLA) in predicting 30-days mortality among hospitalized cirrhotic patients with acute decompensation. The secondary outcome was to determine factors associated with 30-day mortality in cirrhotic patient with acute decompensation.

Statistical analysis

Continuous variables were described as mean-standard deviation (SD) and compared by independent t-test. Categorical variables were described as proportion and compared by using chi-square test. The receiver operating characteristic (ROC) curve analysis of lactate-based serum tests for predicting 30-day mortality was performed, and the area under the ROC curve (AUC) of each score were compared with MELD and MELD-Na for the prediction of 30-day mortality. For the secondary outcome, the uni- and multivariate logistic regression analysis was used to determine the predictive factors of 30-day mortality. Statistical significance was defined as p-value of less than 0.05.

Based on the data from previous study, admission VLAC in hospitalized cirrhotic patients who died and survived within 28 days were 3.9±1.9, and 2±0.55 mmol/L, respectively.[7] Sample size was calculated using STATA version 12 with two-sample for comparison of means. Given that the previously reported 30-day mortality rate in hospitalized cirrhotic patients with acute decompensation was 15%, a total of 74 participants were required.

RESULTS

Baseline demographic data

A total of 74 hospitalized cirrhotic patients with acute decompensation were prospectively enrolled. The mean age was 69.33±13.3 years, with 49 (66.2%) being male. Alcohol consumption (35.1%) was the leading etiology of cirrhosis, followed by chronic hepatitis B infection (18.9%) and non-alcoholic steatohepatitis (17.6%). Regarding the Child-Pugh score, 20 (27%), 34 (46%), and 20 (27%) patients were classified as Child-Pugh A, B, and C, respectively with a MELD score of 18.26±7.04. The main indications for hospitalization were infections (67.6%), followed by gastrointestinal bleeding (18.9%), hepatic encephalopathy (6.8%), and acute kidney injury (4.1%). Among the 50 patients admitted due to infection, 11 (14.9%) had septicemia and 9 (12.2%) had spontaneous bacterial peritonitis. Additionally, 31 patients (41.9%) had acute-on-chronic liver failure (ACLF) upon admission. The detailed baseline characteristics and laboratory values of all the included patients are shown in Table 1.

Clinical outcome

Of the 74 patients included in the study, 22 (29.7%) died within 30 days. The main causes of death were related to infection (81.8%) and, gastrointestinal bleeding (13.6%). Table 1 demonstrates differences in baseline characteristics between those who survived and died within 30 days. The non-survivor group has a higher proportion of ACLF, higher WBC, higher PT, higher aPTT, and lower serum albumin. Regarding the cirrhosis severity scores, MELD and MELD-Na were significantly higher in non-survivor groups (23.91±7.31 vs. 15.87±5.41, P <0.001, and 25.53±7.75 vs. 17.25±7.16, P <0.001, respectively). There was no difference between Child-Pugh score between survivors and non-survivors.

Performance of VLAC, LAC-Cl, MELD-Lactate, and MELD-ΔLA, in predicting 30-day mortality

As shown in Table 2, initial VLAC was significantly higher in non-survivors compared to survivors (9.7±8 vs. 3.61±1.79 mmol/L, P<0.001). In addition, VLAC at 6, 12 and 24 hours were significantly higher in the non-survivor group. However, LAC-Cl at 6, 12 and 24-hour after admission was not significantly different between 30-day non-survivors and survivors. Subgroup analysis was performed in 64 patients who had initial VLAC > 2 mmolL/L, and we found that, LAC-Cl at 24 hours was significantly higher in 30-day survivor group in these patients (32.91±41.42 vs. 2.86±58.23, P=0.023). Regarding the MELD-Lactate and MELD-ΔLA scores, the non-survivors had significantly higher MELD-Lactate, and MELD-ΔLA score at 6 hours compared to those who survived (29.94 ± 6.14 vs. 20.28± 5.37, P <0.001 and 4.05±1vs. 2.06±1.31, P <0.001, respectively). However, there was no significant difference in MELD-ΔLA score at 12 and 24 hours between 2 groups.

The ROC analysis of variable factors for 30-day mortality prediction is demonstrated in Fig 1. As shown, MELD (AUROC 0.81, 95%CI 0.71-0.92), MELD-Na (AUROC 0.77, 95%CI 0.65-0.89), initial VLAC (AUROC 0.79, 95%CI 0.67-0.91), MELD-Lactate (AUROC 0.86, 95%CI 0.77-0.96), and MELD-ΔLA at 6 hours (AUROC 0.86, 95%CI 0.78-0.94) were good predictors of 30-day mortality in cirrhotic patients with acute decompensation. When using MELD score as reference, there was no significant difference in the AUROC of initial VLAC and MELD score in predicting 30-day mortality (P=0.747). Of note, there was a trend toward higher AUROC of MELD-Lactate and MELD-ΔLA score at 6 hours, however, no statistical significance was found.

Factors associated with 30-day mortality

Table 3 shows uni- and multivariable logistic regression analysis of factors associated with 30-day mortality. By univariable analysis, MELD, MELD-Na, initial VLAC, MELD-Lactate, MELD-ΔLA at 6 hours, ACLF on admission, and initial WBC were significantly associated with 30-day mortality. Four models of multivariable analysis were separately performed to avoid collinearity. As shown, all lactate-based tools were independent predictors of 30-day mortality (model 1: VLAC, OR 1.41, P=0.03; model 2: VLAC, OR 1.45, P=0.019, and MELD-Na, OR 1.13, P=0.029; model 3: MELD-lactate, OR 1.29, P<0.001; and model 4: MELD-ΔLA at 6 hours, OR 2.87, P<0.001)

DISCUSSION

This prospective observational study was performed to evaluate the efficacy of various serum lactate-based tests for prediction of 30-day mortality in hospitalized cirrhotic patients with acute decompensation. The main result was the initial VLAC, MELD-Lactate, and MELD-ΔLA at 6 hours were reliable predictors of 30-day mortality in these patients.

Acute hepatic decompensation is one of the most

TABLE 1. Baseline and clinical characteristics of included patients and comparison between 30-day survivors and non-survivors.

Parameters	Overall (n=74)	30-Day survivors (n=52)	30-Day non-survivors (n=22)	P-value*
Age (year, mean ± SD)	69.33 ± 13.30	70.90 ± 13.05	65.63 ± 13.45	0.120
Male (n, %)	49 (66.2%)	34 (65.4%)	15 (68.2%)	0.816
Causes of cirrhosis (n, %):				
Alcoholic	26 (35.1%)	19 (36.5%)	7 (31.8%)	0.902
Chronic hepatitis B	14 (18.9%)	9 (17.3%)	5 (22.7%)	0.827
NASH	13 (17.6%)	4 (7.7 %)	2 (9.1%)	1.00
Cryptogenic	8 (10.8%)	9 (17.3%)	4 (18.2%)	1.00
Chronic hepatitis C	6 (8.1%)	6 (11.5%)	2 (9.1%)	0.758
Child Pugh Score				
A (n, %)	20 (27.0%)	16 (30.8%)	4 (18.2%)	0.408
B (n, %)	34 (45.9%)	24 (46.2%)	10 (45.5%)	0.956
C (n, %)	20 (27.0%)	12 (23.1%)	8 (36.4%)	0.373
Indications for admission:				
Infection (n, %)	50 (67.6%)	34 (65.4%)	16 (72.7%)	0.537
Septicemia	11 (14.9%)	9 (17.3%)	2 (9.1%)	0.489
Spontaneous bacterial peritonitis	9 (12.2%)	6 (11.5%)	3 (13.6%)	1.000
Urinary tract infection	6 (8.1%)	3 (5.8%)	3 (13.6%)	0.354
Pneumonia	9 (12.2%)	6 (11.5%)	3 (13.6%)	1.000
Infective diarrhea	3 (4.1%)	2 (3.8%)	1 (4.5%)	1.000
Gastrointestinal Bleeding (n, %)	14 (18.9%)	10 (19.2%)	4 (18.2%)	1.000
Hepatic encephalopathy (n, %)	5 (6.8%)	4 (7.7%)	1 (4.5%)	1.000
Acute kidney injury (n, %)	3 (4.1%)	2 (3.8%)	1 (4.5%)	1.000
Presence of ACLF:	31 (41.9%)	15 (28.9%)	16 (72.7%)	**0.001**
Grade of ACLF (n, %)				
Grade 1	22 (70.97%)	14 (93.33%)	8 (50%)	
Grade 2	6 (19.35%)	1 (6.67%)	5 (31.25%)	**0.011**
Grade 3	3 (9.68%)	0 (0%)	3 (18.75%)	**0.003**
Laboratory Investigations:				
Complete Blood Count				
White blood cell (/uL, mean ± SD)	9933.78 ± 5849.14	8876.92 ± 4192.79	12904.55 ± 7942.20	**0.026**
Hematocrit (%, mean ± SD)	29.31 ± 7.20	29.44 ± 7.13	28.99 ± 7.53	0.248
Platelet (uL, mean ± SD)	124,702.70 ± 70,079.16	132,884.62 ± 75928.15	105,363.64 ± 50,133.67	0.123
Coagulation test				
PT (sec, mean ± SD)	18.07 ± 5.66	16.35 ± 3.81	22.12 ± 7.19	0.001
PTT (sec, mean ± SD)	40.73 ± 60.77	30.26 ± 8.85	65.48 ± 108.33	**< 0.001**
INR (mean ± SD)	1.56 ± 0.53	1.39 ± 0.35	1.95 ± 0.67	**0.001**
Blood Chemistry				
BUN (mg/dL, mean ± SD)	26.64 ± 16.08	24.49 ± 14.72	31.74 ± 18.27	0.109
Cr (mg/dL, mean ± SD)	1.94 ± 2.13	1.68 ± 1.89	2.55 ± 2.56	0.108

TABLE 1. Baseline and clinical characteristics of included patients and comparison between 30-day survivors and non-survivors. (Continue)

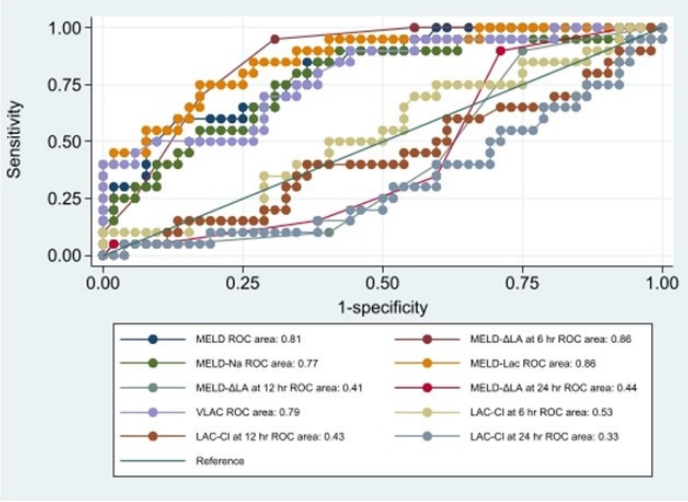
Parameters	Overall (n=74)	30-Day survivors (n=52)	30-Day non-survivors (n=22)	P-value*
Liver function test				
TP (g/dl, mean ± SD)	6.76 ± 1.03	6.85 ± 0.90	6.54 ± 1.27	0.321
Albumin (g/dl, mean ± SD)	2.61 ± 0.62	2.74 ± 0.61	2.31 ± 0.53	0.006
Globulin (g/dl, mean ± SD)	4.10 ± 1.05	4.11 ± 0.93	4.08 ± 1.32	0.926
TB (mg/dl, mean ± SD)	3.71 ± 5.02	3.17 ± 4.70	5.00 ± 5.60	0.153
DB (mg/dl, mean ± SD)	2.51 ± 6.47	2.37 ± 7.32	2.86 ± 3.90	0.764
AST (U/L, mean ± SD)	153.90 ± 311.59	123.65 ± 328.39	225.38 ± 260.76	0.201
ALT (U/L, mean ± SD)	50.47 ± 58.53	40.77 ± 50.8	73.41 ± 69.68	0.027
ALP (U/L, mean ± SD)	146.77 ± 90.65	141.88 ± 93.78	158.32 ± 83.69	0.487
Lactate level (mmol/L, mean ± SD)				
At admission (0 hour, VLAC)	5.42 ± 5.34	3.61±1.79	9.70±8.00	**<0.0001**

*The p-value of <0.05 represents significant difference between survivors and non-survivors.

TABLE 2. Difference in VLAC, LAC-Cl, MELD, MELD-Na, MELD-Lactate, and MELD-ΔLA between 30-day survivors and non-survivors.

Parameters (%, mean ± SD)	30-Day survivors (n=52)	30-Day non-survivors (n=22)	P-value
Lactate level (mmol/L, mean ± SD)			
VLAC/At 0 hour	3.61 ± 1.79	9.70 ± 8.00	**<0.001**
At 6 hours	3.29 ± 1.99	8.1 5± 8.33	**0.002**
At 12 hours	2.93 ± 1.92	8.93 ± 8.96	**<0.001**
At 24 hours	2.48 ± 2.38	7.66 ± 7.72	**<0.001**
Lactate Clearance of all patients (n=74)			
At 6 hours	4.01 ±39.19	10.41 ± 33.86	0.514
At 12 hours	13.63 ± 44.17	2.12 ± 47.54	0.327
At 24 hours	27.49 ± 42.32	2.86 ± 58.23	0.051
Lactate Clearance of patients with initial lactate >2 mmol/L (n=64)			
At 6 hours	6.86 ± 37.73	10.41 ± 33.86	0.717
At 12 hours	20.72±33.88	2.12 ± 47.55	0.078
At 24 hours	32.91 ± 41.42	2.86 ± 58.23	**0.023**
MELD Score (mean ± SD)	15.87 ± 5.41	23.91 ± 7.31	**< 0.001**
MELD-Na (mean ± SD)	17.25 ± 7.16	25.53 ± 7.75	**<0.001**
MELD-Lactate (mean ± SD)	20.28 ± 5.37	29.94 ± 6.14	**< 0.001**
MELD-ΔLA (6 hours) (mean ± SD)	2.06 ± 1.31	4.05 ± 1.00	**< 0.001**
MELD-ΔLA (12 hours) (mean ± SD)	2.88 ± 1.48	2.68 ± 1.21	0.572
MELD-ΔLA (24 hours) (mean ± SD)	2.75 ± 1.52	2.68 ± 1.25	0.853

Abbreviations: VLAC=Venous lactate, LAC-Cl=Lactate clearance, MELD=Model for end stage liver disease, MELD-Lactate= Model for end stage liver disease -lactate, MELD-ΔLA =Model for end stage liver disease lactate clearance, SD=Standard Deviation



Scoring System	Difference AUC	95%CI	P-value (compared to MELD)
VLAC	0.02	(-0.12-0.16)	0.747
LAC-CI at 6 hours	0.28	(0.10-0.47)	0.002
LAC-CI at 12 hours	0.38	(0.18-0.58)	<0.001
LAC-CI at 24 hours	0.48	(0.30-0.67)	<0.001
MELD-Na	0.04	(-0.02-0.11)	0.189
MELD-Lactate	-0.05	(-0.12-0.02)	0.129
MELD- ΔLA (at 6 hours)	-0.05	(0.15-0.05)	0.314
MELD- ΔLA (at 12 hours)	0.40	(0.24-0.56)	<0.001
MELD- ΔLA (at 24 hours)	0.38	(0.23-0.53)	<0.001

Fig 1. AUROC of MELD, MELD-Na, VLAC at admission, lactate clearance, MELD-Lactate, and MELD-Δ LA for 30- day mortality prediction and the differences in AUC of all lactate-based tests when using MELD score as reference.

TABLE 3. Univariate and multivariate analysis of factors associated with 30-day mortality.

Parameters	Univariate analysis		Multivariate analysis							
			Model 1		Model 2		Model 3		Model 4	
	Odd ratio (95%CI)	P-value	Odd ratio (95%CI)	P-value	Odd ratio (95%CI)	P-value	Odd ratio (95%CI)	P-value	Odd ratio (95%CI)	P-value
VLAC	**1.55 (1.17-2.05)**	**0.002**	**1.36 (1.01-1.82)**	**0.041**	**1.39 (1.04-1.86)**	**0.025**	-	-	-	-
MELD	**1.23 (1.10-1.37)**	**<0.001**	**1.15 (1.00 -1.32)**	**0.051**	-	-	-	-	-	-
MELD-Na	**1.16 (1.07-1.26)**	**<0.001**	-	-	**1.14 (1.02-1.27)**	**0.024**	-	-	-	-
MELD-Lactate	**1.32 (1.16-1.50)**	**<0.001**	-	-	-	-	**1.29 (1.12-1.47)**	**<0.001**	-	-
MELD-ΔLA (at 6 hours)	**3.33 (1.90-5.86)**	**<0.001**	-	-	-	-	-	-	**2.87 (1.59-5.18)**	**<0.001**
ACLF at admission	**6.58 (2.16-20.03)**	**<0.001**	2.02 (0.38-10.86)	0.41	2.15 (0.44-10.53)	0.34	1.57 (0.38-6.53)	0.532	2.82 (0.74-10.77)	0.13
WBC	**1 (1.00-1.00)**	**0.009**	1.00 (1.00-1.00)	0.462	1.00 (1.00-1.00)	0.31	1.00 (1.00-1.00)	0.14	1.00 (1.00-1.00)	0.23
Serum albumin	**0.26 (0.09-0.71)**	**0.009**	-	-	-	-	-	-	-	-

Abbreviations: VLAC=Venous lactate, MELD=Model for end stage liver disease, MELD-Lactate= Model for end stage liver disease -lactate, MELD-ΔLA =Model for end stage liver disease lactate clearance, ACLF=Acute-on-chronic liver failure, WBC=White blood cell

common hospitalization causes among cirrhotic patients, which carries an exceptionally high mortality rate. Several laboratory investigations and scoring systems were developed and found to be able to predict mortality in these patients; for example, CTP, MELD, and MELD-Na scores.[3,9,10] Early identification of those with poor prognosis could allow clinicians to timely apply intensive monitoring and treatment protocol. Given that VLAC has been shown to be a simple blood test for determining the severity and prognosis in patients with chronic liver diseases, this parameter could be useful for guiding treatment and initiating early resuscitation in patients who are in acutely decompensated stage.[7] However, the predictive ability of initial VLAC and other lactate-based serum tests in hospitalized cirrhotic patients with acute decompensation has not been well established.

From the pathophysiologic standpoints, lactate levels are elevated in patients with circulatory dysfunction due to both an increase in lactate production and a decrease in lactate clearance. Moreover, because of tissue hypoxemia during a state of shock which limits aerobic metabolism via Kreb's cycle eventually leads to an increase in lactate production, the end metabolic product of anaerobic glycolysis. In the Surviving Sepsis Campaign (SSC)[11], lactate is recommended as part of the SSC Hour-1 sepsis bundle, as well as for pulmonary embolism[12], cardiac surgery[13], and trauma patients.[14] In addition, previous meta-analysis in critically ill patients has demonstrated that lactate level and LAC-Cl are significantly associated with mortality, especially in those with sepsis or septic shock.[15] According to the fact that liver is the primary organ responsible for lactate clearance, prior study has shown that patients with hepatic dysfunction is associated with higher lactate levels.[16] Furthermore, lactate level has been added into scoring systems, with the goal of improving mortality prediction in patients with liver cirrhosis. Our study has clearly demonstrated that serum lactate levels of non-survivors were significantly higher than those of survivors. Furthermore, a recent multicenter trial conducted in critically ill cirrhotic patients has demonstrated the relationship between LAC-Cl after 12 and 24 hours and 28-day survival.[7] This finding all together emphasizes the role of serum lactate as an early prognostic predictor in cirrhotic patients hospitalized due to acute decompensation

The 30-day mortality rate for cirrhotic patients with acute decompensation in the present study was 29.7%, and infection was the major cause of hospitalization and death. This finding is consistent with the results from previous studies.[17] In infected cirrhotic patients, LAC-Cl has been reported to be delayed compared to non-cirrhotic individuals, and the median LAC-Cl within 6 hours in survivors was significantly higher than the non-survivors.[18] Furthermore, in our study, gastrointestinal bleeding was the second most common indication for hospitalization. Interestingly, a recent study in patients with upper gastrointestinal bleeding has demonstrated that higher serum lactate levels within 24 hours of admission was associated with an increase in 7-day rebleeding and 30-day mortality rates.[19-21] On the contrary, another study reported that MELD-Lactate but not lactate level was an effective predictor of in-hospital mortality in cirrhotic patients with variceal and non-variceal gastrointestinal bleeding.[22]

Regarding the prognostic prediction, our study has revealed that MELD, MELD-Na, MELD-Lactate, and MELD-ΔLA at 6 hours were reliable tools for predicting 30-day all-cause mortality in cirrhotic patients with acute decompensation. In terms of MELD-ΔLA, this is the first study reporting the usefulness of MELD-ΔLA at 6 hours for mortality prediction in hospitalized cirrhotic patients. Notably, a previous retrospective study exploring the potential role of MELD-ΔLA for prognostic prediction was based on changes in serum lactate at 48 hours after admission.[8] We propose that if this finding is confirmed in the future studies, prognosis of these patients can be estimated within the earlier timeframe. However, we were not able to demonstrate statistically significant difference in the prognostic ability of VLAC, MELD-Na, MELD-Lactate, and MELD-ΔLA, when compared to the MELD score for mortality prediction. This could be explained by the relatively small number of sample size included in the present study and the mortality rate was higher than being estimated in the sample size calculation.

This study has some limitations. First, this was a single-center study with a relatively small number of sample size; however, the number of participants reached the minimum number determined by sample size calculation. Second, most of our patients were hospitalized due to infection. Considering that infection or sepsis possibly affects the serum lactate level, further studies exploring the difference in the role of serum lactate in cirrhotic patients with and without infection should be of particular interest. Third, our study lacked validation cohort; therefore, these findings need to be redetermined in future studies.

In conclusion, our study has demonstrated that VLAC, MELD, MELD-Na, MELD-Lactate and MELD-ΔLA at 6 hours are simple, useful, and reliable predictors for 30-day mortality in hospitalized cirrhotic patients with acute decompensation. However, no significant difference

in prognostic prediction ability between lactate-based serum tests and MELD score was found.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding source

None

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors contributions

SS designed the study. NK and PB collected the data. NK and SS analyzed the data and drafted the manuscript. PB and SS critically revised the manuscript. All authors gave final approval of the manuscript prior to submission.

List of abbreviations

ACLF: Acute on top chronic liver failure, ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate transaminase, AUROC: Area under the receiver operating characteristic, BUN: Blood urea nitrogen, DB: Direct bilirubin, GI: Gastrointestinal, LAC-Cl: Lactate clearance, MELD: Model for end stage liver disease, MELD-Lactate: Model for end stage liver disease –lactate, MELD-ΔLA = Model for end stage liver disease lactate clearance, NASH: Nonalcoholic Steatohepatitis, PT: Prothrombin time, PTT: Partial thromboplastin time, Cr: Creatinine, SD: Standard Deviation, TB: Total bilirubin, TP: Total protein, VLAC: Venous lactate

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Urine Liver-Type Fatty Acid Binding Protein; Biomarker for Diagnosing Acute Kidney Injury and Predicting Mortality in Cirrhotic Patients

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ABSTRACT

Objective: To determine impact of urine liver-type fatty acid binding protein (uL-FABP) and urine neutrophil gelatinase-associated lipocalin (uNGAL), which were biomarkers linked to acute kidney injury (AKI), in AKI diagnosis and prediction of 28-day mortality among hospitalized cirrhotic patients.

Materials and Methods: We prospectively enrolled hospitalized cirrhotic patients at a tertiary care university hospital between June 2018 and November 2019. The uL-FABP, uNGAL, and plasma NGAL (pNGAL) were collected within 48 hours of admission. Cutoff values of biomarkers for diagnosing AKI derived from receiver operating characteristic (ROC) curve. Logistic regression analysis was used to identify independent factors for 28-day mortality.

Results: We enrolled 109 cirrhotic patients in derivative cohort, 41.3% had AKI. Median uL-FABP, uNGAL, and pNGAL levels in AKI group were higher than non-AKI group: 8.1 vs. 2.8 ng/mL (p=0.002), 40.5 vs. 10.1 ng/mL (p<0.001), and 195.7 vs 81.4 ng/mL (p=0.001), respectively. Areas under the ROC curve of uL-FABP, uNGAL, and pNGAL for AKI diagnosis were 0.68, 0.73 and 0.68, respectively. Also, all biomarkers were significantly higher in mortality group. Multivariate analysis showed that the only independent predictor for 28-day mortality was uL-FABP 4.68 ng/mL (odd ratio 4.15, p=0.02).

Conclusion: UL-FABP, uNGAL, and pNGAL are associated with AKI in hospitalized cirrhotic patients. Moreover, uL-FABP 4.68 ng/mL was a significant independent predictor for 28-day mortality.

Keywords: Acute kidney injury; cirrhosis; liver-type fatty acid binding protein; mortality; neutrophil gelatinase-associated lipocalin; biomarker (Siriraj Med J 2024; 76: 198-208)

INTRODUCTION

Acute kidney injury (AKI) is a common complication in cirrhotic patients. Twenty to fifty percent of hospitalized cirrhotic patients had AKI, which was related to higher mortality and increased length of stay.[1,2] However, the diagnosis of AKI in cirrhotic patients has some limitations, including false low serum creatinine due to low muscle mass and an increase in serum bilirubin, which causes delayed diagnosis.[3]

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Prompt diagnosis of AKI and appropriate treatment in hospitalized cirrhotic patients are essential to reduce short-term mortality.[4] Several urinary biomarkers have been studied for their possible role in early diagnosis and predicting the risk of AKI progression. Among them, neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and liver-type fatty acid binding protein (L-FABP) are currently demonstrated to guide the early diagnosis of AKI and differentiate types of AKI.[5] Urinary biomarkers for the early diagnosis of AKI are applied in several clinical settings other than cirrhosis, for example, post-cardiac surgery, pre-liver transplantation, and mixed intensive care units.[6-11] Recent research in the cirrhosis population has shown that these biomarkers can be utilized to diagnose AKI[12] and differentiate acute tubular necrosis (ATN) from non-ATN in patients with cirrhosis.[12,13]

Two biomarkers for early detection of AKI are L-FABP and NGAL. L-FABP prevents renal ischemic injury by binding to reactive oxygen species (ROS) and excretes them from proximal tubules into urine.[14] NGAL is produced in an ischemic state or after exposure to the renal toxin in tubular cells in thick ascending limbs or collecting ducts.[15] These biomarkers exhibited an increase in level prior to the elevation of serum creatinine, as early as four hours after the onset of AKI.[16] Therefore, this characteristic was more appropriate for the early detection of AKI in comparison to serum creatinine.

Several studies in cirrhotic patients demonstrated the role of urine nGAL (uNGAL) for diagnosis of new-onset AKI in hospitalized cirrhotic patients[17], increased levels of uNGAL and urine L-FABP (uL-FABP) in AKI progression[18], and in mortality group.[19] However, none of these studies evaluated the role of uL-FABP in the early diagnosis of AKI and mortality in cirrhotic patients.

The purpose of this study was to identify the accuracy to determine the relationship between biomarkers, including uL-FABP, uNGAL, and plasma NGAL (pNGAL), for the diagnosis of AKI and association with 28-day mortality in hospitalized cirrhotic patients.

MATERIALS AND METHODS

Patient population

We prospectively enrolled 139 consecutive hospitalized cirrhotic patients with a risk of AKI at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Participants who were admitted between June 2018 and November 2019 were enrolled. Patients were divided into 2 cohorts: 109 patients in derivative cohort, and 30 patients in validation cohort gathered in subsequent 6 months to validate the performance of biomarkers for the diagnosis of AKI and the prediction of mortality. Inclusion criteria included a known diagnosis of cirrhosis, presence of risk of AKI, which included gastrointestinal bleeding, bacterial infection, diarrhea, vomiting, poor intake, large-volume paracentesis, excessive diuretics usage, taking nephrotoxic drugs, decompensated cirrhosis, and age ≥18 years. The exclusion criteria were prior organ transplantation, end-stage renal disease with renal replacement therapy at the time of enrollment, acute interstitial nephritis, acute glomerulonephritis, post-renal AKI, current use of immunosuppressive agents other than treatment of severe alcoholic hepatitis, severe extrahepatic disease, and pregnancy. The protocol was approved by the Institutional Review Board and the Ethics Committee of the Faculty of Medicine, Chulalongkorn University (IRB number 196/61), and was registered at https://www.thaiclinicaltrials.org/show/TCTR20211121002. The registration identification number is TCTR20211121002. All patients, or their legal guardian, gave written informed consent in accordance with the Declaration of Helsinki prior to study enrollment. The manuscript was prepared and revised according to the STARD 2015 checklist.

Study design

Baseline characteristics, clinical data, and laboratory data were obtained within the first 48 hours of admission. The second urine samples and other laboratory data were collected within 48 hours of AKI diagnosis if the patients developed new-onset AKI in admission. Both cirrhotic or other complications were recorded and managed standardly by primary physicians. Patients were follow-up for a minimum of 28 days, and the 28-day mortality rate was recorded.

Sample collection and biomarker measurement

Urine and blood samples were collected within the first 48 hours of admission and centrifuged at 3,000 revolutions per minute (rpm) at 25°C for 10 minutes before being stored at -80°C until assayed. UL-FABP was measured by latex turbidimetric immunoassay using a Norudia® L-FABP (Sekisui Medical CO., Ltd., Tokyo, Japan), with a lower detection limit of 1.5 ng/mL. A UL-FABP level below this value was reported as 0.75 ng/mL. Urine and plasma NGAL were tested by enzyme-linked immunosorbent assay (ELISA) (R&D, Minneapolis, MN, USA). Both results were reported in ng/mL. All biomarker testing was performed by two scientists (JD., ST.) in the critical care laboratory center of nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Definitions of variables

The diagnosis of cirrhosis was based on clinical, imaging, laboratory, or histology assessments. AKI was defined by Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury 2012 as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or an increase in serum creatinine to ≥1.5 times from baseline, which is known or presumed to have occurred within the prior 7 days. We did not use urine volume depletion < 0.5 mL/kg/h for 6 hours as one of the criteria due to inaccuracy of urine output monitoring. AKI in cirrhotic patients is categorized into 3 types. The first is prerenal azotemia, including hepatorenal syndrome (HRS), defined by revised consensus recommendations of the International Club of Ascites 2015[3]; the second is intrinsic renal AKI, including ATN, acute interstitial nephritis (AIN), and glomerulonephritis; and the last post-renal obstruction.[20] Acute on chronic liver failure (ACLF) was defined and graded according to European Association for the Study of the Liver (EASL) criteria.[21] In this study, HRS was separated from prerenal azotemia. Scoring systems including a model for end-stage liver disease (MELD), chronic liver failure-sequential organ failure assessment (CLIF-SOFA), SOFA, and Child-Turcotte-Pugh (CTP) score were calculated at the time of enrollment.

Treatment outcomes

The primary outcome was the performance of uL-FABP, uNGAL, and pNGAL for the diagnosis of AKI compared to creatinine which is a standard of care in hospitalized cirrhotic patients. The secondary outcome was factors in predicting 28-day mortality in hospitalized cirrhotic patients.

Statistical analysis

A sample size of 99 patients was needed to identify AKI using a uNGAL cutoff value 56 ng/mL published in the previous study with 77% sensitivity in diagnosis of AKI, 29% prevalence of AKI in cirrhotic patients[17], for 80% power, and a two-sided α of 0.05. Categorical variables were analyzed by Chi-square or Fisher's exact test, and continuous variables were analyzed by Student's t-test or Mann-Whitney test. Normally distributed variables are reported as the means with standard deviations, and nonnormally distributed variables are reported as medians with interquartile ranges (IQRs). The area under the receiver operating characteristic curve (AUC) was calculated to assess the performance of biomarkers for the diagnosis and discrimination of AKI and the prediction of mortality. Univariate and multivariate logistic regression models were used to evaluate the association between these biomarkers and mortality. All statistical analyses were performed using the SPSS statistical analysis package (version 23.0.0; SPSS Inc., Chicago, Illinois, USA), and a p-value of < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

One hundred and fifty-eight hospitalized cirrhotic patients with a risk of AKI were included. Of these, 19 patients (12%) were excluded due to end-stage renal disease (10 patients, 6.3%), delayed sample collection (3, 1.9%), anuria (3, 1.9%), and incomplete data (3, 1.9%). A total of 139 patients were finally enrolled in the study. We consecutively assigned participants in the whole dataset into a derivation cohort for 109 patients (80%) and a validation cohort for 30 patients (20%) (Fig 1).

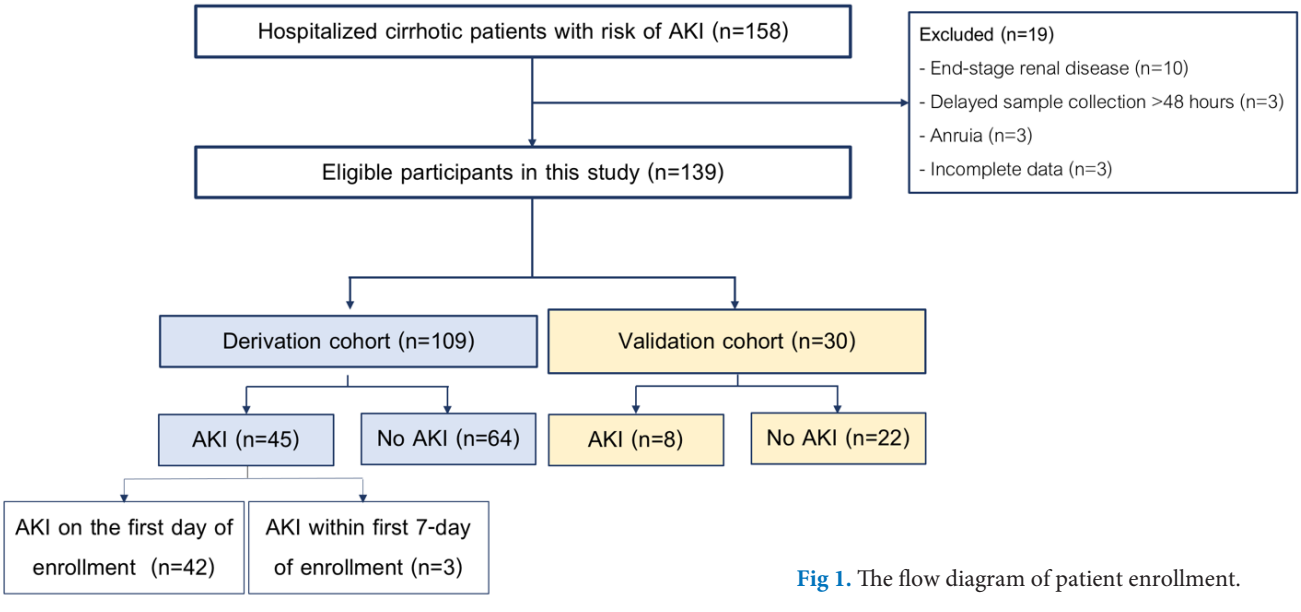

Fig 1. The flow diagram of patient enrollment.

The derivation cohort included a total of 109 patients; 85 (78%) were male, and 51 (46.8%) had CTP class C. The mean age was 59.0±12.3 years, and the median MELD score was 21.0 (IQR 16-27). The most common causes of cirrhosis were alcoholic liver disease (34 patients, 31.2%), followed by chronic hepatitis B (30, 27.5%), chronic hepatitis C (27, 24.8%), and metabolic dysfunction-associated steatohepatitis (7, 6.4%). Fifty-one patients had hepatocellular carcinoma (46.8%). The most common risks of AKI included gastrointestinal bleeding (44, 40.4%), followed by bacterial infection (42, 38.5%), and liver decompensation without identified precipitating causes (11, 10%) (Supplementary Table 1).

The baseline demographic, clinical, and laboratory data of cirrhotic patients with and without AKI were shown in Table 1. A total of forty-five patients had AKI,

TABLE 1. Patient characteristics and baseline laboratory parameters of derivation cohort (n=109).

Variables	Total (n=109)	No AKI (n=64)	AKI (n=45)	p-value
Age (years), mean ±S.D.	59.0±12.3	58.3±12.6	60.1±11.9	0.440
Male sex, n (%)	85 (78%)	50 (78.1%)	35 (77.8%)	0.970
Cause of cirrhosis, n (%)				0.38
HBV/HCV	57 (52.3%)	37 (57.8%)	20 (44.4%)	
Alcohol	34 (31.2%)	18 (28.1%)	16 (35.6%)	
MASH	7 (6.4%)	4 (6.3%)	3 (6.7%)	
Cryptogenic	7 (6.4%)	3 (4.7%)	4 (8.9%)	
Other	4 (3.7%)	2 (3.1%)	2 (4.4%)	
Cancer, n (%)	55 (50.5%)	30 (46.9%)	25 (55.6%)	0.370
HCC	51 (92.7%)	28 (93.3%)	23 (92%)	1.000
Others	3 (5.5%)	1 (3.3%)	2 (8%)	
Laboratory baseline (median, IQR)				
WBC (x10^3/µL)	8.42 (6.65-12.63)	7.83 (6.10-9.89)	9.98 (7.13-14.45)	0.005
% Neutrophil	78 (70.35-84.55)	77.15 (70.17-82.55)	82 (70.4-86.8)	0.045
Neutrophil/lymphocyte ratio	6.2 (3.5-10.0)	5.3 (3.5-8.0)	8.2 (4.1-11.7)	0.011
Platelet (x10^3/µL)	117 (74-178)	106 (68-156)	140 (78-229)	0.041
INR	1.55 (1.37-1.79)	1.5 (1.36-1.66)	1.72 (1.43-2.06)	0.006
Creatinine (mg/dL)	1.0 (0.73-1.44)	0.79 (0.65-1.0)	1.54 (1.24-1.99)	<0.001
Sodium (mmol/L)	133 (128.5-135)	134 (131-137)	131 (127-133)	0.001
TB (mg/dL)	2.73 (1.75-6.43)	2.53 (1.35-4.57)	3.84 (2.13-13.43)	0.003
Albumin (g/dL)	2.6 (2.25-3.15)	2.65 (2.3-3.2)	2.6 (2.1-3.1)	0.240
Lactate (mmol/L)	3.2 (1.6-5.25)	2.05 (1.36-3.4)	4 (2.5-8.7)	0.003
MELD score	21 (16-27)	17 (13.25-22)	28 (22-31)	<0.001
MELD-Na score	22 (17-22)	22 (17-22)	21 (17-28)	0.748
CTP score				0.010
A	17 (15.6%)	15 (23.4%)	2 (4.4%)	
B	41 (37.6%)	25 (39.1%)	16 (35.6%)	
C	51 (46.8%)	24 (37.5%)	27 (60%)	
Plasma NGAL (ng/mL)	125.4 (54.7-251.4)	81.4 (42.2-185.2)	195.7 (80.9-408.4)	0.001
Urine NGAL (ng/mL)	15.1 (6.1-74.7)	10.1 (2.7-26.3)	40.5 (10.4-186.9)	<0.001
Urine L-FABP (ng/mL)	4.2 (2.0-14.3)	2.8 (1.7-8.4)	8.1 (2.6-28.4)	0.002

Abbreviations: AKI; acute kidney injury. CTP; Child-Turcotte-Pugh. HBV; hepatitis B virus. HCC; hepatocellular carcinoma. HCV; Hepatitis C virus. INR; international normalized ratio. IQR; interquartile range. L-FABP; liver-type fatty acid-binding protein. MELD; model for end-stage liver disease. MASH; metabolic dysfunction-associated steatohepatitis. MELD-Na; model for end-stage liver disease-sodium. NGAL; neutrophil gelatinase-associated lipocalin. S.D.; standard deviation. TB; total bilirubin. WBC; white blood cell count.

forty-two (93.3%) had AKI on the first day of enrollment and three (6.7%) patients developed AKI within the first 7 days of enrollment. The most common causes of AKI were prerenal (39 patients, 86.7%), ATN (3, 6.7%), HRS (2, 4.4%), and unclassified (1, 2.2%). The significant laboratories associated with AKI were higher level of white blood cell counts (WBC) (9.98 vs 7.83 x103/μL; p=0.005); percentage of neutrophil (82 vs 77; p=0.045); neutrophil to lymphocyte ratio (NLR) (8.2 vs 5.3; p=0.011); higher INR level (1.72 vs 1.50 mmol/L; p=0.006); higher ALP (178 vs 108; p=0.032); higher both total bilirubin (TB) (3.84 vs 2.53; p=0.003) and direct bilirubin (2.56 vs 1.24; p<0.001), and higher level of venous lactate (4.0 vs 2.0; p=0.003). In addition, the factors associated with AKI in cirrhotic patients were high MELD score (26.9 vs 17.9; p<0.001), and presence of advanced stage CTP C (60.0% vs 4.4%; p=0.010).

The hospital events and complications

The hospital events and complications during hospitalization were shown in Supplementary Table 1. Of 109 patients in derivation cohort, 27 patients (24.8%) expired, 15 patients (13.8%) developed bacterial infection, and 8 patients (7.3%) had organ failure. The rate of hospital-acquired bacterial infection (22.2% vs 7.8%; p=0.803) and new-onset organ failure (13.3% vs 3.1%; p=0.063) during admission were not different between patients with and without AKI. The bacterial infection mostly occurred on the average of day 7 from admission (range 2-27 days). The rate of overall infection was significantly higher in the AKI group than in the non-AKI group (53.3% vs 28.1%; p=0.004). Major sources of infection were spontaneous bacterial peritonitis (SBP) (17 patients, 39.5%), followed by septicemia (10, 23.8%).

Biomarkers and AKI diagnosis

All of 3 biomarkers, pNGAL, uNGAL, and uL-FABP, in patients with AKI were significantly higher than those in patients without AKI as follow: 195.7 vs 81.4 ng/mL (p=0.001), 40.5 vs 10.1 ng/mL (p<0.001), and 8.1 vs 2.8 ng/mL (p=0.002), respectively (Table 1).

The AUC analysis showed that all biomarkers could be used to diagnose AKI in hospitalized cirrhotic patients with comparable accuracy. The AUCs of pNGAL was 0.68 (95% CI 0.57-0.78, p=0.002), uNGAL was 0.73 (95% CI 0.63-0.82, p<0.001), uL-FABP was 0.68 (95% CI 0.57-0.78, p=0.002) compared to creatinine as a standard of care was 0.90 (95% CI 0.83-0.96, p<0.001) for AKI diagnosis (Fig 2A).

The optimal cutoff of each biomarker was determined according to receiver operating characteristic (ROC) curve analysis. The cutoff of uL-FABP was 4.68 ng/mL, providing 68.2% sensitivity and 65.6% specificity; uNGAL was 13.3 ng/mL, with 72.7% sensitivity and 62.5% specificity; and pNGAL was 127.35 ng/mL, with 63.6% sensitivity and 61.3% specificity (Table 2). The combination of multiple biomarkers improved the specificity for the diagnosis of AKI, but the sensitivity was reduced. UL-FABP combined with uNGAL had 56.8% sensitivity and 78.1% specificity, uL-FABP combined with pNGAL had 48.8% sensitivity and 80.6% specificity, and uNGAL combined with pNGAL had 51.2% sensitivity and 74.2% specificity. The combination of all biomarkers had 41.9% sensitivity and 83.9% specificity.

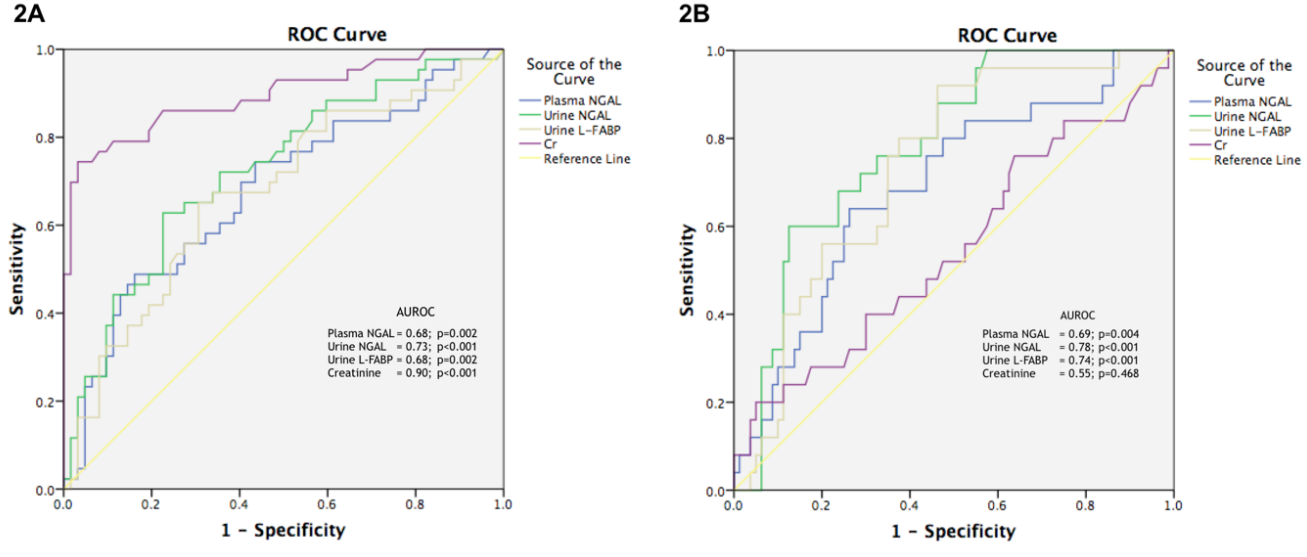

Fig 2A. Performance of pNGAL, uNGAL, uL-FABP, and creatinine for AKI diagnosis in hospitalized cirrhotic patients (n=109). **Fig 2B.** Performance of pNGAL, uNGAL, uL-FABP, and creatinine for predicting 28-day mortality in hospitalized cirrhotic patients (n=109).

TABLE 2. The performance of biomarkers for AKI diagnosis in hospitalized cirrhotic patients in a derivation cohort.

Bio-marker	AUC (95%CI)	p-value	Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
pNGAL	0.68 (0.57-0.78)	0.002	127.35	63.6	61.3	53.8	70.4	1.64	0.59
uNGAL	0.73 (0.63-0.82)	<0.001	13.3	72.7	62.5	57.1	76.9	1.94	0.44
uL-FABP	0.68 (0.57-0.78)	0.002	4.68	68.2	65.6	57.7	75.0	1.98	0.48
pNGAL with CF	0.88 (0.82-0.95)	<0.001	127.35	13.6	100	100	62	0	0.86
uNGAL with CF	0.90 (0.84-0.95)	<0.001	13.3	13.6	100	100	62.7	0	0.86
uL-FABP with CF	0.89 (0.83-0.95)	<0.001	4.68	13.6	100	100	62.7	0	0.86

Clinical factors included bacterial infection, BUN >20, CLIF-OF>10, and MELD score > 20

Abbreviations: AUC; area under the ROC curve. CF; clinical factors. L-FABP; liver-type fatty acid-binding protein. NGAL; neutrophil gelatinase-associated lipocalin. NPV; negative predictive value. PPV; positive predictive value. 95%CI; 95% confidence interval. +LR; positive likelihood ratio. -LR; negative likelihood ratio.

Univariate and multivariate analysis for the AKI diagnosis is shown in Supplementary Table 2. The predictors for the diagnosis of AKI were uNGAL ≥ 13.3 ng/mL (OR 5.75, 95% CI 1.53-21.66, p=0.01), MELD score > 20 (OR 5.03, 95% CI 1.33-19.01, p=0.02), bacterial infection (OR 3.63, 95% CI 1.09-12.09, p=0.04), CLIF-OF score (OR 1.60, 95% CI 1.08-2.36, p=0.02), and BUN (OR 1.07, 95% CI 1.03-1.12, p=0.002). We hypothesized that adding these clinical predictors might improve the accuracy of the studied biomarkers for AKI diagnosis. Clinical factors including presence of bacterial infection, BUN > 20, CLIF-OF > 10, and MELD score > 20 were incorporated into the biomarker in order to assess its sensitivity and specificity. As all clinical factors mentioned were incorporated along with the biomarkers at the optimal cutoff point, the test's specificity and positive predictive value demonstrated an increase in the results, as shown in Table 2. Additionally, the AUC for diagnosing AKI in hospitalized cirrhotic patients increased to 0.89 (95% CI 0.83-0.95) for uL-FABP, 0.90 (95% CI 0.84-0.96) for uNGAL, and 0.88 (95% CI 0.82-0.95) for pNGAL, as shown in Table 2.

According to small number of patients with ATN (3 patients) and HRS (2 patients), there was no significant difference in the levels of each biomarker among patients with prerenal azotemia, ATN, and HRS (p=0.18 for uL-FABP, p= 0.81 for uNGAL, p=0.08 for pNGAL) (Supplementary Table 3).

Biomarkers and prediction of 28-day mortality

Of 109 patients in derivation cohort; the 28-day overall mortality was 24.8%. Patients who died within 28 days after admission had a higher proportion of AKI (70.4% vs 31.7%; p<0.001), presence of cancer (77.8% vs 41.5%; p=0.001), and new-onset organ failure after admission (18.5% vs 3.7%; p=0.02) than those who survived (Supplementary Table 4). Serum sodium was not significantly different between these two groups (133 vs 129, p=0.06). The MELD and CLIF-OF scores were greater in the mortality group; 29 vs 20 (p<0.001) and 9 vs 6 (p<0.001) respectively. The concentrations of the biomarkers uL-FABP, uNGAL, and pNGAL were greater in deceased patients compared to those in survivors; 14 vs 2.72 ng/mL (p<0.001), 104.7 vs 10.3 ng/mL (p<0.001), and 209.3 vs 91.3 ng/mL (p=0.01), respectively.

The AUCs of pNGAL was 0.69 (95% CI 0.57-0.81, p=0.004), uNGAL was 0.78 (95% CI 0.69-0.88, p<0.001), uL-FABP was 0.74 (95% CI 0.64-0.84, p<0.001), and creatinine was 0.55 (95%CI 0.41-0.68, p=0.47) for predicting 28-day mortality (Fig 2B). The performance of all studied

biomarkers for predicting mortality is shown in Table 3. Among them, uL-FABP had the highest sensitivity and specificity to predict 28-day mortality.

By using multivariate analysis, the only independent predictor for 28-day mortality was high uL-FABP ≥ 4.68 ng/mL (OR 4.15, 95%CI 1.21-14.29) (Table 4). There were no clinical factors to predict 28-day mortality; therefore, we combined multiple biomarkers to predict 28-day mortality. The specificity for the predicting mortality was increased, but the sensitivity was reduced. UL-FABP combined with uNGAL had 66.7% sensitivity and 74.1% specificity, uL-FABP combined with pNGAL had 63% sensitivity and 77.8% specificity, and uNGAL combined with pNGAL had 59.3% sensitivity and 68.3% specificity. The combination of all biomarkers had 55.6% sensitivity and 81.5% specificity.

Validation cohort

To validate the role of the performance of biomarkers for the diagnosis and discrimination of AKI and the prediction of mortality, we analyzed an independent cohort of 30 cirrhotic patients consecutively recruited within a subsequent 6-month period. Baseline characteristics of patients in the derivation and validation cohorts were summarized in Supplementary Table 5. All differences between the two cohorts were not statistically significant, with the exception of gender, where males comprised the majority of the derivation cohort and females comprised the majority of the validation cohort. Of 30 patients, 13 (43.3%) were male with mean age 62.8±13.0 years. There were 8 patients (26.7%) who had AKI. The baseline demographic, clinical, and laboratory data of cirrhotic patients with and without AKI of validation cohort were shown in Supplementary Table 6. The performance of biomarkers for AKI diagnosis and prediction of 28-day mortality in the validation cohort were shown in Supplementary Table 7 & 8, respectively.

The AUCs of pNGAL was 0.82 (95% CI 0.66-0.98; p=0.01), uNGAL was 0.76 (95% CI 0.54-0.97; p=0.046), uL-FABP was 0.48 (95% CI 0.22-0.73; p=0.85) compared to creatinine as a standard of care was 0.97 (95%CI 0.92-1.00; p<0.001) for AKI diagnosis (Fig 3A). Moreover, the AUCs of pNGAL was 0.71 (95% CI 0.41-1.00; p=0.13), uNGAL was 0.79 (95% CI 0.55-1.00; p=0.04), uL-FABP was 0.49 (95% CI 0.21-0.77; p=0.93), and creatinine was 0.77 (95% CI 0.58-0.95; p=0.05) for predicting 28-day mortality (Fig 3B).

DISCUSSION

In patients with cirrhosis, AKI is a serious problem that can increase mortality, but the diagnosis is often delayed due to false low serum creatinine levels.[1-3] There is still an urgent need for new biomarkers to diagnose AKI development and poor outcome in hospitalized cirrhotic patients. The three main findings of the study are as follows: 1) baseline uL-FABP, uNGAL, and pNGAL are related to AKI and 28-day mortality in hospitalized patients with cirrhosis, 2) uNGAL demonstrated fair discriminating ability in diagnosing AKI, in contrast to pNGAL and uL-FABP. However, combining clinical factors with these biomarkers was able to improve their accuracy for AKI diagnosis. The discriminating ability to predict 28-day mortality was shown to be fair only for uNGAL and uL-FABP, but not for pNGAL. 3) Baseline

TABLE 3. The performance of biomarkers for prediction of 28-day mortality in hospitalized cirrhotic patients in a derivation cohort.

Biomarker	AUC (95%CI)	p-value	Cut-off (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
pNGAL	0.69 (0.57-0.81)	0.004	127.35	68.0	56.8	32.7	85.2	1.58	0.56
uNGAL	0.78 (0.69-0.87)	<0.001	13.3	77.8	56.8	37.5	88.5	1.81	0.39
uL-FABP	0.74 (0.64-0.84)	<0.001	4.68	81.5	63.0	42.3	91.1	2.19	0.29

Abbreviations: AUC; area under the ROC curve. L-FABP; liver-type fatty acid-binding protein. LR; likelihood ratio. NGAL; neutrophil gelatinase-associated lipocalin. NPV; negative predictive value. PPV; positive predictive value. 95%CI; 95% confidence interval. +LR; positive likelihood ratio. -LR; negative likelihood ratio.

TABLE 4. Univariate and multivariate analysis for prediction of 28-day mortality in hospitalized cirrhotic patients.

Factors	Univariate analysis OR (95%CI)	p-value	Multivariate analysis OR (95%CI)	p-value
Age	1.02 (0.98-1.06)	0.30		
Bacterial infection	1.61 (0.67-3.87)	0.29		
AKI	5.11 (1.98-13.20)	0.001	2.20 (0.71-6.77)	0.17
Biomarkers				
pNGAL ≥ 127.35 ng/mL	3.04 (1.19-7.72)	0.02	1.56 (0.48-5.03)	0.46
uNGAL ≥ 13.3 ng/mL	4.60 (1.68-12.61)	0.003	1.64 (0.46-5.81)	0.45
uL-FABP ≥ 4.68 ng/mL	7.48 (2.56-21.82)	<0.001	4.15 (1.21-14.29)	0.02
uNGAL≥ 13.3 ng/mL and uL-FABP ≥ 4.68 ng/mL	5.71 (2.23-14.66)	<0.001		
Laboratories baseline				
Neutrophil/lymphocyte ratio	1.02 (0.99-1.05)	0.11		
INR	3.47 (1.40-8.57)	0.01		
Creatinine	1.43 (0.89-2.31)	0.14		
Sodium	0.93 (0.86-1.01)	0.06		
Sodium < 130 mmol/L	3.57 (1.43-8.90)	0.01	2.60 (0.87-7.75)	0.09
ACLF grade				
1	2.58 (0.67-9.83)	0.17		
2	5.15 (1.30-20.37)	0.02		
3	12.88 (2.25-73.71)	0.004		
MELD > 20	3.33 (1.22-9.11)	0.02		
SOFA	1.27 (1.05-1.53)	0.01		
New-onset organ failure	5.98 (1.33-27.02)	0.02	4.30 (0.68-27.07)	0.12

Abbreviations: ACLF; acute-on-chronic liver failure. AKI; acute kidney injury. CTP; Child-Turcotte-Pugh. INR; international normalized ratio. IQR; interquartile range. L-FABP; liver-type fatty acid-binding protein. MELD; model for end-stage liver disease. NGAL; neutrophil gelatinase-associated lipocalin. SOFA; Sequential Organ Failure Assessment.

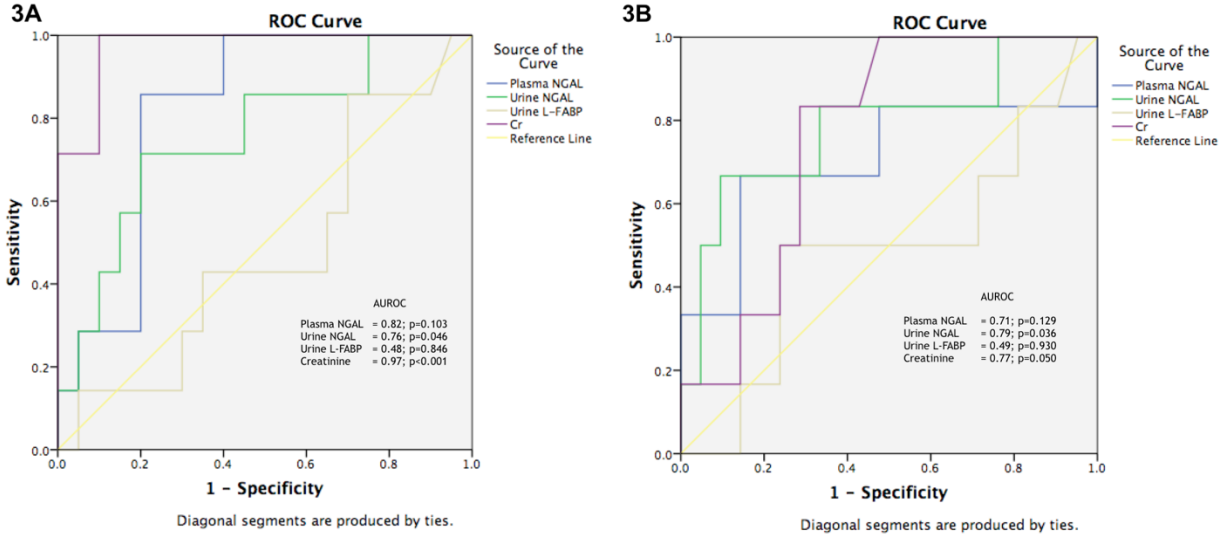

Fig 3A. Performance of pNGAL, uNGAL, uL-FABP, and creatinine for AKI diagnosis in hospitalized cirrhotic patients in the validation cohort (n=30). **Fig 3B.** Performance of pNGAL, uNGAL, uL-FABP, and creatinine for predicting 28-day mortality in hospitalized cirrhotic patients in the validation cohort (n=30).

uL-FABP was an independent predictor of 28-day mortality in hospitalized patients with cirrhosis and may be useful to guide clinicians for close monitoring and early management.

There was a clear association between the levels of the biomarkers tested and the occurrence of AKI or 28-day mortality. The levels of uL-FABP, uNGAL, and pNGAL were considerably greater in cirrhotic patients with AKI or death compared to cirrhotic patients who did not experience AKI or death. This is consistent with a previous study by Treeprasertsuk S. et al[17] that showed the advantage of using uNGAL in predicting AKI and poor outcomes. However, a recent study by Jiang QQ et al. demonstrated that there were no significant differences in uL-FABP and uNGAL levels between decompensated cirrhosis patients with AKI and those without AKI.[22] This result differed from our research. The possible reason is the difference in sample selection criteria. We included both decompensated and compensated cirrhosis in the AKI and non-AKI groups, whereas Jiang QQ et al included ACLF and decompensated cirrhosis in their study.

In our study, the performance of uL-FABP for prediction of death was found to be comparable to that of uNGAL. However, from multivariate analysis, only baseline uL-FABP was able to independently predict 28-day mortality. This could be explained by the different pathophysiology of both urine biomarkers. UL-FABP was demonstrated to have a linear correlation with hypoperfusion and liver injury, whereas uNGAL correlated with systemic inflammation and sepsis.[23] This current study included both infected and noninfected patients, and the majority were in the noninfected group, for instance, gastrointestinal bleeding and liver decompensation (Supplementary Table 1), which hypothesized hypoperfusion and liver injury. Moreover, the majority of deceased patients was in the non-infectious group, this data provided further support why uL-FABP and not NGAL was the sole predictor of mortality in this study. The finding that hospitalized cirrhotic patients with baseline uL-FABP ≥ 4.68 ng/mL had a 4-5-fold higher mortality risk than those with uL-FABP < 4.68 ng/mL with 81.5% sensitivity and 63% specificity was consistent with the results of a previous study which established that uL-FABP independently predicted AKI progression and mortality during admission.[18] From this information, uL-FABP might be useful for identifying high-risk patients for fatal outcomes and encouraging prompt management to reduce morbidity and mortality. However, due to insufficient sample size, the results of the validation cohort were not replicable.

The clinical features and laboratory profiles of cirrhotic patients at baseline also influenced their outcomes. Multivariate analysis from our data showed that MELD score > 20, CLIF-OF score, presence of bacterial infection, and BUN were independent predictors of AKI development. Interestingly, the previous study demonstrated the utility of NLR in predicting bacterial infection and short-term mortality[24] although our outcome was not as predicted. NLR did not reach statistical significance for prediction of 28-day mortality. We postulated that NLR representing dysregulation of the immune system in cirrhosis and/or decompensation especially the suppression of T lymphocytes, hence the majority affecting this biomarker was an infection-related complication. Though, less than half of the patients in our cohort had infectious causes, NLR was not a well providing prognostic marker in our study.

Additionally, we further evaluated the performance of AKI diagnosis and predicting mortality when combining these clinical parameters with biomarkers. The combination of these clinical factors improved the AUC of biomarkers from 0.67 to 0.89 for uL-FABP, 0.72 to 0.90 for uNGAL, and 0.68 to 0.88 for pNGAL in AKI diagnosis. When combining the clinical factors with biomarkers, the highest AUC achievable was 0.90 with uNGAL for AKI diagnosis. The specificity and positive predictive value of the test also improved. The prior study evaluated the association between the number of urine biomarkers (L-FABP, NGAL, IL-18, and albumin) above the cutoff for AKI development and mortality, as well as relative risk for the outcome.[18] As the number of biomarkers exceeding the threshold increased, so did the relative risk for AKI development and mortality. Thus, we investigated whether combining two biomarkers would improve their diagnostic sensitivity and specificity for AKI diagnosis and predicting mortality. The results showed that using two out of three biomarkers resulted in decreased sensitivity and increased specificity, which improved the reliability of the test for AKI diagnosis and prediction of 28-day mortality.

The validation cohort was established with the purpose of confirming the effectiveness of these biomarkers in mortality prediction and AKI diagnosis. In the validation cohort, uL-FABP lacked the ability to differentiate AKI or predict 28-day mortality owing to its AUC being less than 0.5. One potential constraint was the relatively small sample size of the validation cohort, which contained a relatively low proportion of individuals with AKI (26.7% vs. 41.3%, p=0.14) in comparison to the derivative cohort.

Regarding the differentiation of subtypes of AKI, this study included a small number of patients with ATN and HRS, and the levels of each biomarker did not differ significantly between subtypes of AKI. Thus,

more study is essential to determine the significance of biomarkers in diagnosing subtypes of AKI.

Finally, our study had some limitations. First, this study was a single-center study with sufficient sample size; however, the number of cirrhotic patients presenting with ATN or HRS was insufficient to establish a definitive conclusion regarding their ability to distinguish between the two conditions. Second, serum creatinine for the diagnosis of AKI might be underestimated and inaccurate for the diagnosis due to low muscle mass and increased serum bilirubin in cirrhotic patients.[3] And lastly, the small number of validation cohort limited the study's replicability. A future study that includes a larger number of patients in the AKI group should be explored to assess the effectiveness of the biomarker in predicting outcomes within this specific population.

CONCLUSION

Our prospective cohort study showed that structural urinary biomarkers were significantly higher in cirrhotic patients with AKI and with 28-day mortality. UNGAL for AKI diagnosis and uL-FABP for predicting mortality was shown to be acceptable. Together with clinical factors, these biomarkers had a better discriminating performance for the diagnosis of AKI than biomarkers alone. Furthermore, baseline uL-FABP ≥ 4.68 ng/mL was a valid predictor of 28-day mortality in hospitalized cirrhotic patients.

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Author contributions

Study concept and design (SW, NS, ST), acquisition of data (SW, TT, RC, PK, PT, ST), analysis and interpretation of data (TP, KT, CP), drafting of the manuscript (SW, TP), critical revision of the manuscript for important intellectual content (NS, TT, KT, ST), administrative, technical, and material support (NS, ST), and study supervision (NS, ST).

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Conflict of interest statement

All authors declare no conflict of interest, no plagiarism, no fabrication, and no falsification.

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Effect of Delayed Endoscopic Retrograde Cholangiopancreatography after Diagnosis of Acute Cholangitis; A Real-life Experience

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ABSTRACT

Objective: Acute cholangitis is a potentially life-threatening condition. Its main treatments include antibiotics and biliary drainage, but longer waiting times for endoscopic biliary drainage may be unavoidable in some limited-resource settings.

Materials and Methods: All patients who presented with cholangitis and received ERCP during the 3-year study period were included. The associations between waiting time from the diagnosis of acute cholangitis to the endoscopic drainage and the clinical outcomes, including 30-day all-course mortality and 30-day rehospitalization rates, were compared in patients who received ERCP within 24 hours, 48 hours, 72 hours, 7 days, and later than 7 days.

Results: Overall, 300 patients were included. The 30-day all-course mortality rate was 5%, with 9% overall rehospitalization rate, and median waiting time for ERCP of 5 days (1 -50 days). There was no significant difference between 30-day mortality rates in patients who received ERCP within 24 hours, 48 hours, 72 hours and over 7 days ($p > 0.05$). The mortality rate was significantly higher in those with severe cholangitis and with pancreatobiliary malignancy ($p < 0.05$).

Conclusion: In real life situation when resources are limited, delayed ERCP did not increased the 30-day mortality rate in patients with cholangitis.

Keywords: Cholangitis; ERCP (Siriraj Med J 2024; 76: 209-215)

INTRODUCTION

Acute cholangitis is a common emergency condition in clinical practice, and it carries a high rate of morbidity and mortality if not properly treated. According to the Tokyo Guidelines (2018), patients who present with cholangitis should be classified into 3 levels of severity: mild, moderate, and severe.[1] Antibiotics and supportive care are recommended for all patients, but those with mild cases of the disease do not always require biliary drainage. On the other hand, patients with moderate forms of the disease require early drainage, and severe cases need it urgently.[2] Unfortunately, some types of biliary drainage, such as endoscopic retrograde cholangiopancreatography (ERCP), require special expertise and equipment which are not available in every hospital in Thailand; in most of these cases, after initial treatment, patients are referred to a center in which the procedure is available, resulting in a delay in performance of the procedure. Several studies have recommended conducting ERCP within 24 hours of diagnosis of cholangitis[3,4], but others have

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shown no survival benefits of early endoscopic drainage.[5] As a result, we conducted a retrospective study of the clinical impact of the timing of ERCP in patients with acute cholangitis and its clinical outcomes in settings with limited resources.

MATERIALS AND METHODS

We retrospectively reviewed all patients who were diagnosed with acute cholangitis and received ERCP in our institute between May 2018 and April 2021. Those with incomplete clinical information were excluded. Baseline characteristics, severity of cholangitis, etiology of biliary obstruction, and timing of ERCP after the diagnosis of cholangitis were analyzed. The waiting time in all patients were counted from the first presentation of acute cholangitis to the time of ERCP. The patients were classified in accordance with the physical status classification of the American Society of Anesthesiologists (ASA). The clinical outcomes, including 30-day mortality, 30-day rehospitalization rate, and length of hospital stay (LOS) were investigated. Unfortunately, information relating to length of hospital stay was missing for some patients who were referred from other hospitals specifically for ERCP. The study protocol was approved by local ethics committee.

Statistics or analysis or statistical analyses

The statistical software SPSS version 22.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses. All tests were two-tailed and $p < 0.05$ was considered significant. Descriptive analysis was presented as median (IQR), and categorical data, such as the correlation between timing of ERCP and 30-day mortality and rehospitalization, were analyzed using Chi-square test. Comparison of continuous data, such as LOS, was performed using Man-Whitney U- test. The univariate and multivariate analysis were calculated using logistic regression analysis.

RESULTS

After exclusion of those with incomplete data, a total of 300 patients were included and analyzed, and their baseline characteristics are shown in Table 1. The mean age was 61 years old, with equal proportions of females and males. The majority of the patients (58.3%) had comorbid diseases, with hypertension, diabetes mellitus and dyslipidemia being the three most common. All patients presented with clinical acute cholangitis and were diagnosed with cholangitis at the time of presentation and received standard care for acute cholangitis, such as intravenous antibiotics, intravenous fluid, and other supportive management.

TABLE 1. Baseline characteristics of the patients included in the study.

Characteristics	Total (n=300)	
	n	%
Sex		
Male	150	50.0%
Female	150	50.0%
Age (years) Mean±SD.	61.36 ±18.08	
<40	42	14.0%
40-49	38	12.7%
50-59	44	14.7%
60-69	63	21.0%
70-79	60	20.0%
≥80	53	17.7%
Comorbid Disease		
No	125	41.7%
Yes	175	58.3%
Hypertension	127	42.3%
Diabetes	90	30.0%
Dyslipidemia	31	10.3%
Coronary artery disease	12	4.0%
Chronic kidney disease	8	2.7%
Cerebrovascular disease	7	2.3%
Thalassemia	8	2.7%
Malignancy	6	2.0%
Other	26	8.7%
ASA score		
1	137	45.7%
2	124	41.3%
3	39	13.0%

Abbreviation: ASA = American Society of Anesthesiologists (ASA) physical status classification

The majority (58%) of the patients had mild cholangitis triggered by common bile duct stones (59.7%). The most common cause of malignant biliary obstruction was cholangiocarcinoma, followed by ampullary cancer. The mean interval for ERCP after the diagnosis of acute cholangitis was 8 days. Most of the patients were admitted with sepsis, and 7% developed septic shock. The incidence of 30-day mortality was 5%, mean length of hospital stay was 6 days, and the readmission rate was 9% (Table 2).

TABLE 2. Acute cholangitis presentation and complications according to each level of severity (n = 300).

	Total	Mild (%)	Moderate (%)	Severe (%)
Severity	300	174 (58.0%)	103 (34.3%)	23 (7.7%)
Malignant Obstruction				
No	238 (79.3%)	154	69	15
CBD stone	179 (59.7%)	117	51	11
Strictures	59 (19.7%)	37	18	4
Yes	62 (19.7%)	20	34	8
Cholangiocarcinoma	25 (8.3%)	6	14	5
Ampulla	20 (6.7%)	11	8	1
Pancreas	14 (4.7%)	2	10	2
Gallbladder	3 (1.0%)	1	2	0
Time to ERCP (days)				
Median (IQR)	5.0 (3-10)	7 (1 -50)	4 (1-47)	2 (1-22)
< 24 hours	33	16	11	6
24 -48 hours	39	14	16	9
48-72 hours	40	19	18	3
72 hours to 7days	83	43	37	3
> 7 days	105	82	21	2
Hospital Course				
Sepsis	199 (66.3%)	102	94	3
Septic shock	21 (7.0%)	1†	1	19
Respiratory failure	13 (4.3%)	1	1	11
Acute kidney injury	4 (1.3%)	0	0	4
DIC	2 (0.7%)	0	0	2
30-Day Mortality	15 (5.0%)	3 (1.7%)	5 (4.9%)	7 (30.4%)
Length of stay (Median±IQR)	5.0 (2-7)	4.0 (2-6.5)	6.0 (5-8)	10.0 (6-17)
Rehospitalization	27 (9.0%)	10	15	2

Abbreviations: IQR = interquartile range, SD = standard deviation, DIC = dissemination intravascular coagulation
†sepsis occurred as a consequence of hospital-acquired infection

Length of hospital stay was shorter than the waiting time from onset of cholangitis to ERCP, since most patients were diagnosed in other institutes and then referred to our hospital. Mortality occurred in 15 cases, a rate of 5%.

Table 3 shows the number of cases of 30-day mortality by each severity level and waiting time. There was significant correlation between the waiting time and 30-day mortality in patients with mild cholangitis (P = 0.05) but no significant difference mortality in overall severity was observed. Regarding other factors that relate to the mortality, the incidence of 30-day mortality was significantly associated with the severity of cholangitis and the presence of malignant obstruction (p-value <0.05) but showed no significant correlation with age, ASA status, or total bilirubin, with p-values of 0.99, 0.7 and 0.2, respectively. There were 3 cases of mortality after mild cholangitis, and the causes of death were progression of underlying pancreatobiliary malignancy in 2 patients, and hospital-acquired infection after the treatment of acute cholangitis in one case. Table 4 showed the mortality rate when patients received ERCP according to each cut-off point. Overall, performance of ERCP within 7 days showed a difference in overall lower

TABLE 3. Association between 30-day mortality and waiting time for ERCP according to cholangitis severity.

Severity of cholangitis	Timing					P value
	< 24 hours	24 to 48 hours	48 to 72 hours	72 hours to 7 days	>7 days	
Mild (N = 174)	0	0	0	3	0	0.05
Moderate (N = 103)	0	0	1	2	2	0.66
Severe (N = 23)	2	2	1	2	0	0.55
Total (N = 300)	2	2	2	7	2	0.37

TABLE 4. Associations between 30-day mortality, rehospitalization rate, and waiting time for ERCP according to cholangitis severity at each cut-off point.

Severity of cholangitis	24 hours			48 hours			72 hours			>7 days		
	≤ 24 hours	>24 hours	P value	≤ 48 hours	>48 hours	P value	≤ 72 hours	>72 hours	P value	≤7 days	>7 days	P value
Mortality												
Mild	0/16 (0%)	3/158 (1.9%)	1.00	0/30 (0%)	3/144 (2.1%)	1.00	0/49 (0%)	3/125 (2.4%)	0.56	3/92 (3.3%)	0/82 (0%)	0.25
Moderate	0/11 (0%)	5/92 (5.4%)	1.00	0/27 (0%)	5/76 (6.6%)	0.32	1/45 (2.2%)	4/58 (6.9%)	0.38	3/82 (3.7%)	2/21 (9.5%)	0.27
Severe	2/6 (33.3%)	5/17 (29.4%)	1.00	4/15 (26.7%)	3/8 (37.5%)	0.66	5/18 (27.8%)	2/5 (40%)	0.60	7/21 (33.3%)	0/2 (0%)	1.00
Overall	2/33 (6.1%)	13/267 (4.9%)	0.77	4/72 (5.6%)	11/228 (4.8%)	0.80	6/112 (5.4%)	9/118 (4.8%)	0.83	13/195 (6.7%)	2/105 (1.9%)	0.07
Rehospitalization												
Mild	1/16 (6.3%)	9/158 (5.7%)	0.93	3/30 (10%)	7/144 (4.9%)	0.27	3/49 (6.1%)	7/125 (5.6%)	0.89	9/92 (9.8%)	1/82 (1.2%)	0.02
Moderate	1/11 (9.1%)	14/92 (15.2%)	0.59	2/27 (7.4%)	13/76 (17.1%)	0.22	5/45 (11.1%)	10/58 (17.2%)	0.38	13/82 (15.9%)	2/21 (9.5%)	0.46
Severe	1/6 (16.7%)	1/17 (5.9%)	0.46	1/15 (6.7%)	1/8 (12.5%)	1.00	2/18 (11.1%)	0/5 (0%)	1.00	2/21 (9.5%)	0/2 (0%)	1.00
Overall	3/33 (9.1%)	24/ 267 (9%)	0.99	6/72 (8.3%)	21/228 (9.2%)	0.82	10/112 (8.9%)	17/188 (9%)	0.97	24/195 (12.3%)	3/105 (2.9%)	0.01

mortality, but this did not reach statistical significance (P = 0.07). The Kaplan-Meier curve demonstrating cumulative 30-day survival according to each severity and waiting time for ERCP using 7 days at the cut-off point is demonstrated in Fig 1. Performance of ERCP within 7 days was associated with a significant difference in rehospitalization rate, especially in mild cases but with a higher rehospitalization rate in early procedure (Table 4). For all severity levels, shorter waiting times for ERCP reduced the length of hospital stay, especially for those who received ERCP early and in those with mild forms of the disease (Table 5). However, hospital stay in our center might not represent total treatment course since most cases of ERCP were performed as outpatient care and the patient were admitted after the procedure.

Considering the factors that associated with 30-day mortality, we performed the univariate and multivariate analysis (Table 6). The univariate analysis did not show clinical significance correlation between age, ASA status or the waiting time interval for ERCP but there was significant correlation with severe cholangitis and the presence of pancreatobiliary malignancy. There was marginal correlation between the waiting time when considered as a continuous data. When these parameters are calculated using multivariate analysis, there was no significant correlation between the waiting time before ERCP but still demonstrated significant correlation between the mortality rate and the presence of malignancy and severe cholangitis.

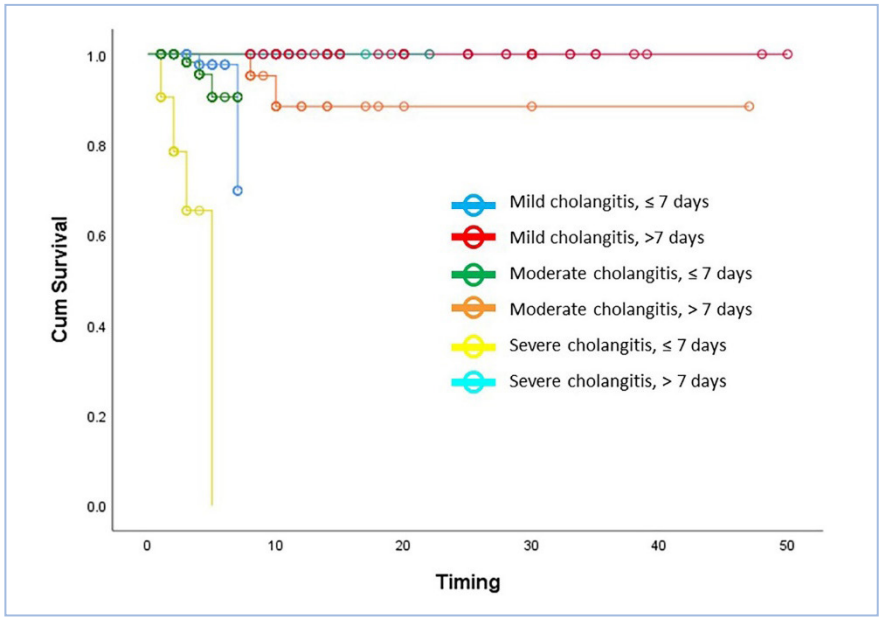

Fig 1. Kaplan-Meier curve demonstrating cumulative 30-day survival according to each severity and waiting time for ERCP using 7 days at the cut-off point.

TABLE 5. Associations between length of stay (data presented as median (IQR)) and waiting time for ERCP according to cholangitis severity.

Severity of cholangitis	Timing						
	< 24 hours	24 to 48 hours	48 to 72 hours	72 hours to 7 days	>7 days	Total	P value
Mild (N = 174)	6.00 (3.00-7.75)	5 (3.00-6.00)	5 (4.00-9.00)	6.00 (4.00-7.00)	2 (2.00-3.25)	4.00 (2.00-6.25)	< 0.05
Moderate (N = 103)	5.00 (5.00-6.00)	5.00 (5.00-7.00)	6.00 (5.75-8.25)	6.00 (5.00-7.50)	8.00 (4.50-12.50)	6.00 (5.00-8.00)	0.09
Severe (N = 23)	12.00 (6.75-24.00)	10.00 (4.50 -19.50)	6.00 (5.00-6.00)	9.00 (3.00-9.00)	6.00 (2.00-6.00)	10.00 (6.00-17.00)	0.39
Total (N = 300)	6.00 (4.50-7.50)	5.00 (4.00-8.00)	6.00 (4.00-8.75)	6.00 (4.00-8.00)	2.00 (2.00-7.00)	5.00 (2.00-7.00)	< 0.05

TABLE 6. Univariate and multivariate analysis predicting 30-day mortality.

Factors	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	P value
Age	1.03 (0.99-1.06)	0.137	-	
ASA score			-	
1	1			
2	1.11 (0.349 – 3.54)	0.860		
3	1.82 (0.43 – 7.63)	0.413		
Presence of Malignant obstruction	8.76 (2.87-26.68)	< 0.001	8.61 (2.43-30.52)	0.001
Severity				
Mild	1		1	
Moderate	2.91 (0.68-12.43)	0.150	1.34 (0.29-6.19)	0.707
Severe	24.94 (5.87 – 105.92)	< 0.001	14.47 (3.10 – 67.55)	0.001
Timing	0.91 (0.81 – 1.02)	0.099	0.93 (0.815 -1.05)	0.225
Time interval	0.85 (0.59- 1.23)	0.395	-	-

DISCUSSION

Acute biliary infection, particularly acute cholangitis, can cause rapid deterioration in a patient's condition, and it warrants prompt and proper treatment. In addition to appropriate administration of antibiotics, timely biliary drainage via endoscopic transpapillary biliary drainage is also important.

There have been several studies of the differences in outcomes achieved after different lengths of waiting times for performance of ERCP following the onset of cholangitis, and their results have varied. An older nationwide study of clinical outcomes of patients with cholangitis who were admitted during weekdays or at weekends and received delayed ERPC showed no differences in length of stay, mortality, or total cost of hospitalization[6], underlining the importance of supportive treatment. More recently, another large nationwide retrospective study conducted in the USA found that performing ERCP within 48 hours lowered in-hospital mortality, 30-day mortality, and readmission rates for all levels of severity.[7] On the other hand, research in Japan and Taiwan showed that ERCP within 48 hours after diagnosis lowered the incidence of mortality only in cases of moderate severity and did not affect mortality in mild or severe cases.[1] These data were included in a meta-analysis involving 7534 patients which demonstrated lower odds of 30-day mortality (OR, 0.39; 95% CI, 0.14-1.08) and organ failure (OR, 0.69; 95% CI, 0.33-1.46) when the patients received ERCP within 48 hours.[8] Focusing only on severe cholangitis, two retrospective studies showed conflicting results. One study from China showed that performing ERCP later than 48 hours after diagnosis of severe acute cholangitis was associated with a longer ICU stay but not with in-hospital or 30-day mortality. In this report, performance of biliary drainage within 24 hours did not significantly reduce the mortality or shorten ICU stay.[9] On the other hand, another retrospective study showed that biliary drainage within 12 hours was beneficial for patients with neurological or cardiovascular dysfunction, and the authors recommended complete biliary decompression within 24 hours of admission for severe acute cholangitis.[10]

However, ERCP, which is the method of choice for biliary drainage, requires special equipment and advanced technical skill on the part of the physician. In limited-resource situations, patients who are diagnosed with acute cholangitis need to be transferred to a center where ERCP is available; hence, the waiting time for this procedure might be different from that recommended in the treatment guidelines.

Our study investigated the effect of waiting time for ERCP in patients with cholangitis, a common occurrence in centers with limited resources. We analyzed the correlation

between waiting time and 30-day all-course mortality, length of hospital stay, and 30-day rehospitalization. Our results showed that the waiting time for ERCP did not affect 30-day mortality but shortened the length of hospital stay. Also, there was a significant difference in rehospitalization rate when ERCP was performed within 7 days but the number of those who received earlier ERCP showed a higher rehospitalization rate. Interestingly, the 30-day mortality rate in patients who received early ERCP was higher than delayed ERCP. The main reason is unknown but this might be due to the selection bias as attending physicians may decide to perform ERCP earlier in more severe cases or cases with comorbidity. Furthermore, our findings were slightly different from those of previous studies, as we had a low number of patients in the severe cholangitis group compared with those with mild or moderate forms of the disease. Considering the univariate and multivariate analysis for the factors that associated with 30-day mortality, there was no significant correlation between the waiting time for biliary drainage but significant mortality rate become high when a patient has severe cholangitis or has a pancreatobiliary malignancy. This analysis correlates with our finding that 2 out of 3 patient with mild cholangitis died from the underlying malignancy shortly after the procedure.

Our study had several limitations. Firstly, it included only those who received ERCP for biliary drainage. Patients with acute cholangitis who underwent other methods, such as percutaneous tube placement, or who died before the endoscopic procedure, were not included in the study. Secondly, the length of hospital stay in our study might not be accurate, since many patients were admitted from the primary care hospital specifically for the procedure or referred for the ERCP as an outpatient care. Thirdly, as this study is based on retrospective analysis, many missing data might be present. As our study showed many conflicting data, these findings should be confirmed in a larger study cohort.

CONCLUSION

In conclusion, in real life situation when resources are limited, delayed ERCP did not increase the 30-day mortality rate in patients with cholangitis. The 30-day mortality was higher with severe cholangitis and pancreatobiliary malignancy.

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None

Conflict of interest

None

Authors contribution

Study design: TC, Data gathering:PK, data source: TC, KL, AS, TR, Drafting the manuscript: TC, statistics: TC, Revision and comment: TC, KL, AS, TR.

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The Influence of Medical Subspecialty on the Adherence to Hepatocellular Carcinoma Surveillance in Patients with Chronic Hepatitis B

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ABSTRACT

Objective: This study aimed to determine the adherence rate of HCC surveillance in CHB patients at the largest tertiary hospital in Southern Thailand and identify patient and physician factors that influence it.

Materials and Methods: This retrospective cohort study included patients with CHB who were followed up for more than 1 year between 2011 and 2019 at a tertiary care hospital in Thailand. Patients diagnosed with HCC within 6 months of their first visit were excluded. The rate of adherence with HCC surveillance was calculated using percentage of time up-to-date with HCC surveillance (PTUDS).

Results: The mean age of 531 eligible patients at the time HCC surveillance started was 55.5 ± 9.26 years. The most common indications for surveillance were male over 40 years of age (41.2%), female over 50 years of age (28.9%), and cirrhosis (22.6%). The median PTUDS was 70.6% (interquartile range 55.1 – 81.4%). The highest PTUDS was for cirrhosis (74.0%). For physicians' subspecialties, the median PTUDS was 71.8% for gastroenterologists (IQR 58.3 – 81.6%) and 41.7% for internists (IQR 31.4 – 65.8%). Factors associated with increased PTUDS by multivariable analysis were having ≥2 clinical visits per year (±18.4%, p<0.001), civil servant reimbursement (±8.81%, p=0.001), cirrhosis (±6.06%, p=0.003), and being follow-up by gastroenterologists (±20.4%, p<0.001).

Conclusion: The adherence with surveillance program in patients with CHB being followed up at a tertiary care setting in Thailand was good. This finding underscores the importance of education regarding indications for HCC surveillance, particularly in patients without cirrhosis.

Keywords: Hepatocellular carcinoma; surveillance; hepatitis B; adherence; compliance (Siriraj Med J 2024; 76: 216-224)

INTRODUCTION

Chronic hepatitis B (CHB) infection is a public health concern worldwide. In 2015, there were approximately 275 million people living with CHB.[1] In Thailand, approximately 2.9 to 5.1% of the population, or up to 3 million people, had CHB.[2,3] CHB significantly increases the risk of developing hepatocellular carcinoma (HCC) and accounts for 32% of all causes of HCC worldwide and 50% in Thailand.[4,5]

HCC is the second most common cause of cancer-related mortality worldwide.[4] The American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver (APASL) recommend that patients at high-risk of developing HCC (e.g., those with CHB-related cirrhosis) should enter a surveillance program consisting of ultrasonography with or without the measurement of the serum alpha-

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fetoprotein (AFP) level every 6 months to enable the treatment of potentially treatable disease.[6-8] Despite this recommendation, the surveillance rate remains low at approximately 20% in the US, up to 65% in the UK, and approximately 26% in China.[9-12]

The HCC surveillance rate in Thailand is unknown. In this study, we aim to assess the HCC surveillance rate and compliance in patients with CHB in Thailand, and to identify patient and physician characteristics that could influence the HCC surveillance rate and compliance in such patients.

MATERIALS AND METHODS

Study design and patient population

This retrospective cohort study included consecutive patients with CHB who were monitored for at least one year at Songklanagarind Hospital, a tertiary care university hospital in Thailand between January 2011 and December 2019. The start date of 2011 was chosen to allow time for implementation of the 2010 AASLD guidelines, which include HCC surveillance every 6 months. Patients with CHB were included in the study if they were eligible for HCC surveillance according to the AASLD or EASL recommendations as follow: 1) male aged 40 years or older and female aged 50 years or older, 2) adult patients (aged 18 years or older) with CHB who had a family history of HCC in their first-degree relative(s), and 3) CHB-related cirrhosis.[6,7] If two or more surveillance indications were met, the patients would be categorized for the indication associated with the highest risk of HCC according to the AASLD guideline. CHB patients were identified via the Hospital Information System using the International Classification of Diseases Tenth (ICD-10) Revision codes, and the eligibility of each patient was determined after chart review. Demographic, clinical, and surveillance data were retrieved by the Division of Digital Innovation and Data Analytics (DIDA), Faculty of Medicine, Prince of Songkla University, and double-checked by investigators.

The study was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkhla University, Songkhla, Thailand (REC.63-189-14-4). The informed consent was waived by the HREC due to retrospective study of de-identified patients. This research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

All CHB diagnoses by ICD-10 were verified by laboratory results of having positive HBsAg or HBV DNA on two occasions, 6 months apart, or review of the physicians' note of the diagnosis of CHB in medical records. Patients with cirrhosis were defined by either histologically, radiologically, non-invasive measurement of liver stiffness by transient elastography of more than 12.5 kPa, or having cirrhotic complications such as ascites, hepatic encephalopathy, and esophageal varices. HCC was diagnosed and staged according to the 2018 AASLD criteria.[6]

The exclusion criteria were follow-up time at our center for less than 1 year, diagnosis of HCC within 6 months of the first visit, or imaging not performed at Songklanagarind Hospital.

Definitions of surveillance and adherence

Surveillance was defined as liver imaging, including ultrasonography, computed tomography, or magnetic resonance imaging, performed every 6 months according to the AASLD and EASL guidelines with or without measurement of the serum alpha-fetoprotein level.[6,7]

The rate of adherence with surveillance program was assessed using the percentage of time up-to-date with surveillance (PTUDS).[9] To calculate the PTUDS, a patient was credited with 6 months of surveillance following any hepatobiliary imaging. The 6-month clock was restarted if a test was performed before completion of the previous 6-month interval. For example, a patient who was followed-up from January 1, 2019 to December 31, 2019 and had abdominal ultrasound performed on January 1, 2019 and December 30, 2019 would be categorized as being up-to-date with surveillance for 66.7% of his or her follow-up period (12/18 months).

The follow-up duration was defined as the time between the visit at which the study inclusion criteria were deemed to be met and the last day of follow-up until December 2019 or to the date of diagnosis of HCC plus a 6-month credit thereafter.

Study variables

Several variables assumed to have an influence on PTUDS were pre-selected: sex, age (including age at the time of diagnosis and age at the time of starting surveillance), reimbursement status, family history of HCC in first-degree relative(s), indication for HCC surveillance, background medical comorbidities, physician's subspecialty, and travel distance. The physicians' subspecialties were categorized into internal medicine (defined as not having the Thai Board of Gastroenterology certification, but certified Thai board of Internal Medicine), gastroenterology (board-certified internists who were in training for or already had received Thai Board of Gastroenterology certification) Travel distance (defined as the distance between the center of the patient's residential area to Songklanagarind Hospital) was modeled as a continuous

variable and categorized into quintiles based on an estimated duration of travel by car.

Statistical analysis

We calculated the sample size required using the finite population mean formula. With a population size of 5,000 (from total hospital number with diagnosis of CHB) and a standard deviation derived from Goldberg *et al.* of 21.5, along with an error margin of 2, we determined a sample size of 408 while maintaining a significance level of 0.05 and a power of 0.80.

Descriptive statistics were used; categorical variables were reported as number (percentage) and continuous variables were reported as mean+SD or median (interquartile range [IQR]). To compare PTUDS among groups, we used either the Mann-Whitney U-test or Student's t-test as applicable. A univariable linear regression model was used to estimate the beta coefficient and 95% confidence interval (CI) for each variable to predict its relationship with the continuous outcome of PTUDS. All variables with a p-value <0.05 from univariate analyses were then included in the multivariable linear regression model. All statistical analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria, 2021).

RESULTS

Patient characteristics

We screened 542 patients by ascending hospital number. Of these, total 531 patients with CHB who were followed up for more than a year and fulfilled an indication for HCC surveillance were eligible for the study. The sex distribution was slightly male predominant (male 54.5%, female 45.5%) (Table 1). The mean age of the patients at an initiation of surveillance program was 55.5 ± 9.26 years and the median follow-up duration was 7.6 (IQR 4.5 - 9.0) years. The median number of clinical visits for CHB per year was 3.4 (IQR 2.7 - 4.3). The most common reimbursement scheme was civil servants (71.4%). Ten percent of the cohort had a family history of HCC in first-degree relatives. The most common indications for surveillance were male sex and age 40 years or older (41.6%), female sex and age 50 years or older (29.0%), and cirrhosis (22.6%). Family history of HCC was the sole indication for surveillance in only 6.8% of the entire cohort.

Most of the patients in the cohort was free of medical comorbidities at baseline. Hypertension and diabetes mellitus were the leading co-underlying diseases in 20.3% and 13.3%, respectively. The patients were followed up by gastroenterology subspecialists (88.9%) more than by internal medicine specialists (11.1%).

HCC surveillance adherence rates

The median PTUDS in an entire cohort was 70.6% (IQR 54.9 - 81.4%). Cirrhosis was the indication with the highest rate of PTUDS at the median PTUDS of 74.0%, compared with 68.9% for the remaining indications (Fig 2). The median PTUDS for the internal medicine subspecialty was 41.7% (IQR 30.1 – 68.2%) and that for gastroenterology was 71.8% (IQR 58.2 – 81.6%) ($p < 0.001$). Among gastroenterologists, the median PTUDS was 76.5% for hepatologists vs. 69.0% for non-hepatology gastroenterologists ($p < 0.001$). (Fig 3)

The overall compliance rate for the patients to the surveillance program was 97.2%, with 443 patients (83.4%) had 100% compliance rate, 68 patients (12.8%) had compliance rate of 80% or more, and 20 patients (3.8%) had less than 80%.

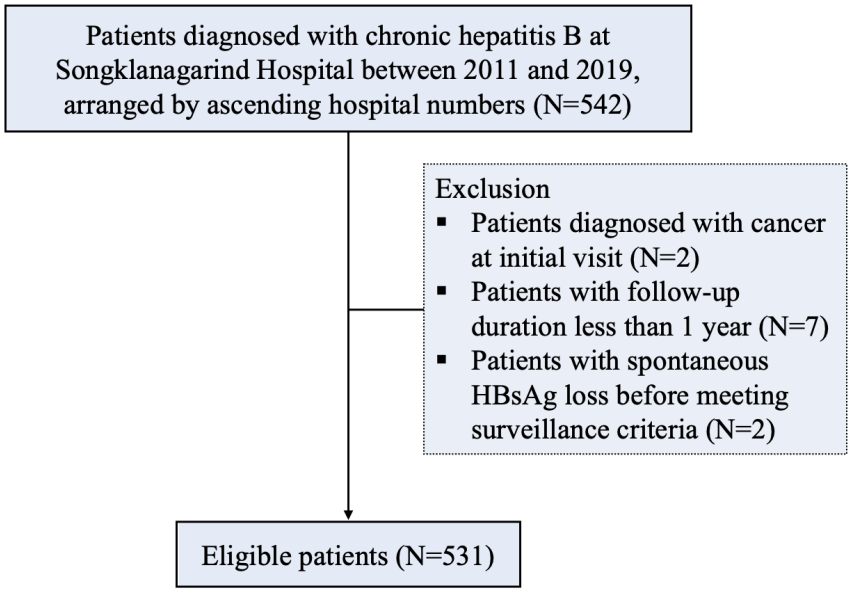

Fig 1. Study flow

TABLE 1. Patient demographic and clinical characteristics.

Variables	Total (n = 531)
Male Sex, n (%)	290 (54.5%)
Age at diagnosis (years)	49.0±12.0
Age at surveillance (years)	55.5±9.26
Visits per year, n (%)	
1-2	330 (62.2%)
>2-4	32 (6.0%)
>4	169 (31.8%)
Travel distance quintile (km), n (%)	
0–40	248 (46.6%)
41–100	83 (15.6%)
101–180	119 (22.6%)
181–300	68 (12.8%)
>301	13 (2.4%)
Reimbursement, n (%)	
Self Payment	55 (10.3%)
Universal Coverage	79 (14.9%)
Civil Servant	379 (71.4%)
Social Security	18 (3.4%)
Family History of HCC[a], n (%)	55 (10.4%)
Indication, n (%)	
Male, age 40 years or older	221 (41.6%)
Female, age 50 years or older	154 (29.0%)
Family history of HCC	36 (6.8%)
Cirrhosis	120 (22.6%)
Underlying disease, n (%)	
Hypertension	108 (20.3%)
Diabetes mellitus	71 (13.3%)
Cardiovascular disease	9 (1.69%)
Chronic kidney disease	8 (1.50%)
Stroke	1 (0.19%)
Cancer[b]	25 (4.70%)
HBV/HCV co-infection	4 (0.75%)
HIV	11 (2.06%)
Specialty, n (%)	
Internal medicine	59 (11.1%)
Gastroenterology or hepatology	472 (88.9%)

Quantitative variables are expressed as the mean and standard deviation and categorical variables as the count and proportion. [a]First-degree relative. [b]All cancers except HCC. HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus

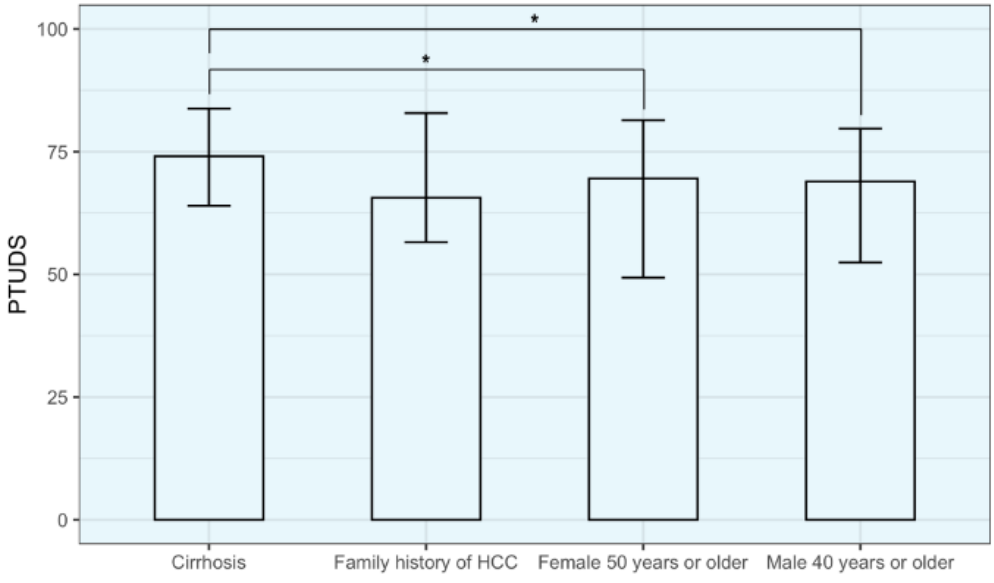

Fig 2. Median PTUDS by Surveillance Indication; *P<0.05; PTUDS: percentage of time up-to-date to HCC surveillance

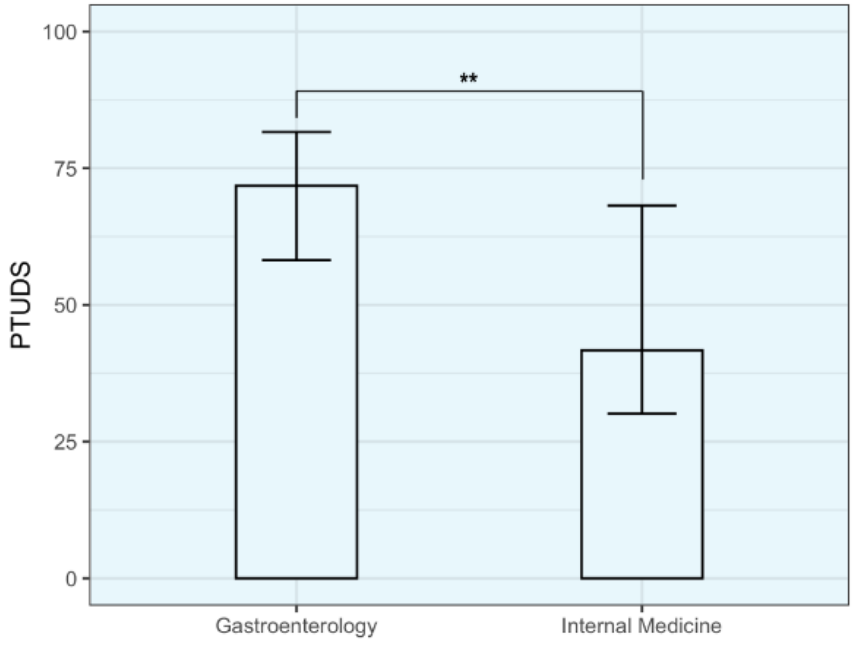

Fig 3. Median PTUDS by Physician's Subspecialty; **P<0.001

Factors associated with HCC surveillance

Univariate analyses of factors associated with an increased HCC surveillance rate revealed that more-than-two clinical visits per year, the civil servant reimbursement scheme, cirrhosis as the surveillance indication, and gastroenterology subspecialty were significant positive predictors (Table 2). Having Human immunodeficiency virus (HIV) co-infection was significantly associated with a lower HCC surveillance rate in the univariate analysis. Age at the time of surveillance initiation and travel distance quintile were not a significant predictor of surveillance rates.

When factors that were significant in univariate analyses were evaluated in the multivariable analysis, more-than-two clinical visits per year, the civil servant reimbursement scheme, cirrhosis as an indication for surveillance, and being followed-up with gastroenterology specialists remained significantly associated with an increased HCC surveillance rate (Table 2). However, HIV comorbidity was no longer statistically significant in the multivariable analysis.

Incidence and characteristics of HCC

HCC was detected during surveillance imaging in

TABLE 2. Factors associated with surveillance of hepatocellular carcinoma.

Variables	Univariable analysis		Multivariable analysis	
	Beta coefficient (95% CI)	P values	Beta coefficient (95% CI)	P values
Male Sex	-0.82 (-4.39 to 2.75)	0.65		
Age at diagnosis	0.12 (-0.03 to 0.26)	0.12		
Age at surveillance				
<40	Reference	0.06		
≥40	8.71 (-0.59 to 18.0)			
Visits per year		<0.001		
1-2	-19.0 (-26.4 to -11.6)	<0.001	-18.4 (-25.3 to -11.6)	<0.001
>2-4	Reference		Reference	
>4	0.55 (-3.24 to 4.33)	0.78	-0.13 (-3.69 to 3.43)	0.94
Travel distance (km)		0.91		
0-40	Reference			
41-100	-0.69 (-5.90 to 4.52)			
101-180	1.10 (-3.48 to 5.67)			
181-300	-1.33 (-6.95 to 4..29)			
>301	-3.21 (-14.9 to 8.47)			
Reimbursement		0.008		
Self-Payment	Reference		Reference	
Civil Servant	10.0 (4.16 to 15.9)	<0.001	8.81 (3.48 to 14.2)	0.001
Social Security	11.0 (0.02 to 15.9)	0.049	9.59 (-0.51 to 19.7)	0.06
Universal Coverage	7.21 (0.08 to 14.3)	0.047	5.65 (-1.02 to 12.3)	0.10
Family History of HCC[a]	-0.14 (-5.82 to 5.54)	0.96		
Indication		<0.001		0.003
Non-cirrhosis	Reference		Reference	
Cirrhosis	7.19 (2.97 to 11.4)		6.06 (2.09 to 10.0)	
Underlying disease				
Hypertension	-1.93 (-6.34 to 2.48)	0.39		
Diabetes mellitus	-1.62 (-6.84 to 3.60)	0.54		
Cardiovascular disease	8.29 (-5.46 to 22.0)	0.24		
Chronic kidney disease	-0.08 (-14.7 to 14.5)	0.99		
Stroke	8.02 (-33.0 to 49.0)	0.70		
Cancer[b]	1.94 (-6.45 to 10.3)	0.65		
HBV/HCV co-infection	-11.2 (-34.9 to 12.5)	0.35		
HIV	-23.5 (-35.9 to -11.2)	<0.001	-11.0 (-22.9 to 0.88)	0.07
Specialty		<0.001		<0.001
Internal medicine	Reference		Reference	
Gastroenterology	20.1 (14.7 to 25.5)		20.4 (14.8 to 25.9)	

[a]First-degree relative. [b]All cancers except HCC. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; CI, confidence interval

13 patients (2.4%) accounting for incidence rate of 3.7 per 1,000 person-years. Classifying patients by indication for surveillance, 2 were male aged 40 years or older, 1 was female aged 50 years or older, and 10 were cirrhosis. The mean PTUDS for these patients was 75.9 ±13.1%. All of them had been under the care of a gastroenterologist at the time of diagnosis of HCC. Four of these 13 patients (30.4%) developed HCC in a non-cirrhotic liver. The mean time interval between the start of surveillance and diagnosis of HCC was 4.4 years. Almost all of the HCCs detected (12 out of 13) were very early to early stage (Barcelona clinic liver cancer staging 0 to A).

DISCUSSION

This retrospective study is the first to report the rate of adherence with HCC surveillance in patients with CHB in Thailand. For a median follow-up duration of 7.6 years, the median overall adherence with HCC surveillance as defined by PTUDS in our study was 70.6%, which was quite decent compared with previous reports. Goldberg et al. reported the mean PTUDS of any liver imaging in patients with cirrhosis in the US to be 23.3% with a mean follow-up duration of 4.7 years.[9] The strongest predictor of adherence in their study was being followed-up by a specialist in gastroenterology or infectious diseases. The difference between the mean PTUDS in the study by Goldberg et al. and that in our cohort probably reflects a difference in the study population and the clinical setup, as the patients in the study by Goldberg et al. were diagnosed with cirrhosis of various etiologies and followed up at their local hospital, whereas the majority of our patients being diagnosed with non-cirrhotic CHB and followed up at the tertiary-care referral center. One of the factors associated with increased PTUDS was similar, namely, a number of specialty visit, although most specialists in our cohort were gastroenterologists. However, a study by Tran et al. conducted at a university medical center also reported a low rate of adherence with HCC surveillance in patients with chronic hepatitis C cirrhosis, as only 24.4% underwent HCC surveillance every 6 months and 44% received HCC surveillance every 12 months.[10] Interestingly, Asian ethnicity was a predictor of a better surveillance adherence in the study by Tran et al., which might be associated with the increased PTUDS rate in our study, as all of our patients in the cohort were Asian. A recent systematic review of cohort studies evaluated the HCC surveillance rate reported similar results, with an overall surveillance rate of 24.0% and a pooled surveillance rate of 73.7% in studies that included subspecialty care.[13]

The factors associated with a higher adherence rate in our study, such as cirrhosis as an indication for surveillance and follow-up by gastroenterology specialists, underscore the importance of knowledge gap regarding indications for HCC surveillance in high-risk groups, especially the non-cirrhotic population. Thus, implementing an educational program for physicians on HCC surveillance and indications might be beneficial in increasing adherence rates within the community. These findings are also in line with those of other studies.[14-17] The patient-reported barriers associated with receipt of HCC surveillance revealed in other studies were also demonstrated in our study.[18,19]

To further improve the adherence rate of the surveillance program based on our findings, scheduling patients for more than two clinical visits per year could increase the possibility of ultrasound being performed every six months and potentially improve the patient-doctor relationship in the process. The finding that reimbursement scheme of civil servant exhibited higher adherence rates compared to other group was unsurprising due to the ease of medical access to our institution. For instance, patients with universal coverage scheme were required to obtain a referral letter from their local hospital once every year before visiting our center. Interestingly, the distance patients traveled to the hospital did not significantly impact adherence in our study, possibly due to all patients in our cohort being from the lower southern regions of Thailand.

This study had several strengths. First, in contrast with most of the previous studies, which have only reported the surveillance rate in cirrhotic populations, we assessed the HCC surveillance rate in both non-cirrhotic and cirrhotic patients with CHB. Second, the median follow-up duration in our cohort was long and reflected the real-world clinical scenario. Third, this is the first study to report the rate of adherence with HCC surveillance in Thailand, and the findings can be used to improve awareness of the need for surveillance in the country.

The study also had several limitations. Our study was conducted at a single referral center, so its results may not be generalizable to other health care systems. The indications for imaging during the follow-up period were not limited to the surveillance purpose and could include computed tomography performed for an evaluation of the abdominal organs as of other medical or emergency conditions. Therefore, the PTUDS may have been overestimated in some patients. Additionally, the time interval between a clinic appointment and imaging, which has been shown to be associated with the likelihood of adherence with surveillance, was not

investigated. However, almost all imaging ordered in our cohort was eventually performed. Lastly, since this study was a retrospective cohort utilizing the hospital information system from Songklanagarind Hospital, there were no records of education level or economic status available for retrieval, which might influence adherence to HCC surveillance.

In conclusion, we found that the adherence rate to HCC surveillance in our cohort was 70.6%. This study demonstrated the importance of the literacy regarding indications for HCC surveillance, especially in non-cirrhotic patients and those who were not under the care of a gastroenterology specialist. These findings could further guide the implementation of health policy to increase the dissemination of HCC surveillance nationwide and contribute to improved patient survival.

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Declarations

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None to declare.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author's contributions

PF and NC made substantial contributions to the study concept and design, collecting data, analysis and interpretation of data, and drafting of the manuscript. PS, SJ, and AK made substantial contributions to interpretation of data and critical revision of the article. All authors contributed to critical revisions and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkhla University, Songkhla, Thailand (REC.63-189-14-4). The informed consent was waived by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkhla University due to retrospective study of de-identified patients. This research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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Current Perspectives on Small Bowel Tumors: Overview of Prevalence, Clinical Manifestations, and Treatment Approaches

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ABSTRACT

Small bowel tumors (SBTs) constitute a rare yet increasingly recognized group of gastrointestinal neoplasms, accounting for less than 5% of all gastrointestinal cancers. Despite their infrequency, the incidence of SBTs has exhibited a notable upward trend, underscoring the importance of understanding these diverse and complex tumors. This review consolidates current knowledge on SBTs, encompassing epidemiology, risk factors, clinical manifestations, diagnostic advancements, and treatment modalities. Data from various sources are analyzed to present a comprehensive overview of the evolving landscape of SBTs. Our findings indicate that adenocarcinomas, carcinoid tumors, lymphomas, and gastrointestinal stromal tumors (GISTs) are the common SBTs. While adenocarcinoma and neuroendocrine tumors are the common types of SBTs in the West, GIST and lymphoma are more common in Asia. Common risk factors include genetic syndromes and inflammatory bowel diseases. There is variability in clinical presentations depending on the type of tumors. Although diagnostic challenges persist, advancements in imaging and endoscopic techniques have improved detection rates. Treatment strategies are evolving; surgical resection remains the mainstay for localized disease, augmented by systemic therapies and targeted agents for advanced stages. This review emphasizes the importance of early detection and individualized treatment approaches in improving outcomes for SBT patients. It addresses the need for ongoing research and innovation in managing these tumors.

Keywords: Small bowel tumors; adrenocarcinoma; gastrointestinal stromal tumors; neuroendocrine tumors; small bowel lymphoma (Siriraj Med J 2024; 76: 225-233)

INTRODUCTION

Small bowel tumors (SBT) are rare and have historically been responsible for less than 5% of gastrointestinal neoplasms. Nevertheless, the incidence of small intestinal cancer has increased over time and is associated with significant morbidity. Approximately 40 different histological types of tumors have been identified, and approximately two-thirds of those represent malignant diseases such as adenocarcinoma, carcinoid tumor, lymphoma, and gastrointestinal stromal tumor (GIST). This article aims to describe small bowel tumors, including epidemiology, risk factors, clinical manifestations, diagnosis, and treatment.

The rising incidence of small intestinal cancers and their varied histological presentation presents a complex challenge in clinical management and patient care, elevating the importance of understanding their epidemiology, risk factors, clinical manifestations, diagnosis, and treatment strategies. This surge reiterates the need for heightened awareness and advanced diagnostic approaches and calls for an in-depth exploration into the evolving dynamics

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of small bowel tumors. This article aims to address these critical aspects, offering a perspective on small bowel tumors to inform and guide clinical practice in this changing landscape.

Epidemiology and types of small bowel tumors

In the US, small bowel tumors account for 0.5% of all cancers. The estimated annual incidence of SBTs demonstrated 2.3 cases per 100,000 inhabitants and has increased over time.[1,2] The results from SEER-9 data, which includes 22,082 patients with small bowel cancers between 1976-2016, demonstrate that the incidence of small intestinal cancers more than doubled in the period from 12.1 to 27.9 per million. Most of this increase was neuroendocrine tumors, which increased from 3.7 to 14.6 per million.[3] In the UK, the overall small bowel tumor incidence rate also doubled from the early 1990s to 2014. The rate of new small bowel tumor cases has increased with an average of 1.9-2.4% per year over the last ten years.[4]

In symptomatic patients, small bowel tumors are important etiologies. It is the second leading cause in patients with obscure gastrointestinal (GI) bleeding (8.8%) and the fourth leading cause in those presenting with small bowel obstruction (5%).[5,6]

The prevalence of different histological subtypes varies across studies are presented in Fig 1. According to US data derived from the National Cancer Database from 1985-2005, the most common type of small bowel tumor is carcinoid tumor, which accounts for 37.4% of cases, followed by 36.9% for adenocarcinomas, 17.3% for lymphomas, and 8.4% for stromal tumors.[7] In the French cancer registry, adenocarcinoma is the most common histological type (38%), followed by neuroendocrine tumors (35%), lymphoma (15%), and sarcoma (12%).[8] Interestingly, GIST is more common in Asia than in the West and is the most common SBT in Thailand, accounting for 39.5% of cases, followed by adenocarcinoma (25.9%) and Lymphoma (24.3%).[9] Furthermore, a study from Taiwan also reports that GIST is common, accounting for 27.5% of small bowel tumors. The other common tumors are the same, including adenocarcinoma (26.1%) and lymphoma (29%).[10]

Risk factors of small bowel tumors

The risk factors for small bowel tumors are summarized in Table 1.[11-13]

Hereditary Mutations Linked to Small Bowel Tumors

1. Familial Adenomatous Polyposis (FAP): Characterized by a germline APC mutation, FAP significantly increases the risk of adenoma polyps growing and transforming into adenocarcinoma by the age of 40. The small intestine is notably the second most common site for adenocarcinoma in individuals with FAP, with a risk 330 times higher than the general population. Jagelman's study, which included 1255 FAP patients, found that 5% developed small bowel adenocarcinoma, predominantly in the duodenum.[2,12]

2. Lynch Syndrome: This hereditary defect in mismatch repair is known for increasing the risk of non-polyposis colorectal carcinoma. The relative risk for developing small bowel adenocarcinoma in those with Lynch syndrome, especially with the MLH1 mutation, ranges from 25 to 291 times that of the general population, though the lifetime risk remains low at about.[2,12]

3. Peutz-Jeghers Syndrome (PJS): Resulting from autosomal dominant inheritance involving a mutation

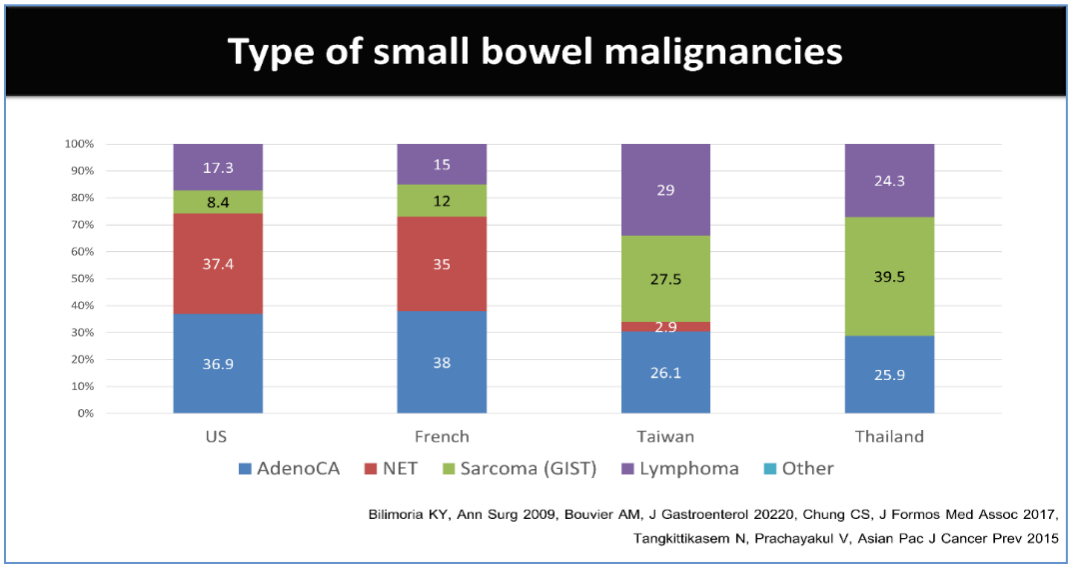

Fig 1. Types of small bowel tumors in different cohorts.

TABLE 1. Risk factors for small bowel tumors.

Type	Conditions	Risk
Adenocarcinoma	FAP	330x
	HNPCC (Lynch syndrome)	25-291x
	PJS	520x
	Crohn's disease	SIR 22x, prevalence 0.23%
		Most common at ileum
		0.2% after 10 y, 2.2% after 25 y
	Celiac disease	10-13x
NET	MEN1	5-10% of NET in GI tract
	NF-1	2-4x
Sarcoma(GIST)	NF-1	2-4x
Lymphoma	Celiac disease	

Abbreviations: FAP, familial adenomatous polyposis; GIST, gastrointestinal stromal tumor; HNPCC, hereditary nonpolyposis colorectal cancer; MEN1, multiple endocrine neoplasia syndrome type 1; NET, neuroendocrine tumor; NF-1, neurofibromatosis ype 1; PJS, Peutz-Jeghers Syndrome; SIR, standard incidence ratio

in the STK11 (SK11) gene, PJS increases the likelihood of individuals developing hamartomatous polyps within the gastrointestinal tract, with the relative risk of encountering small bowel tumors being 520 times greater than that observed in the general population.[2,12]

4. Multiple Endocrine Neoplasia Syndrome Type 1 (MEN1): Caused by an autosomal dominant defect in the MEN1 gene, this syndrome significantly predisposes individuals to neuroendocrine tumors (NETs) of the upper GI tract, representing 5-10% of all GI NETs.[12,14]

5. Neurofibromatosis Type 1 (NF1): An autosomal dominant defect in the NF1 gene, NF1 increases the risk of developing NET and sarcoma by 2-4 times in affected patients.[12,14]

6. Inflammatory Bowel Disease (Crohn's Disease): An autoimmune disorder causing widespread intestinal inflammation, most commonly in the ileum. Patients with Crohn's disease have a 17 to 41 times increased risk of developing small bowel adenocarcinoma, with a cumulative risk of 0.2% after 10 years and 2.2% after 25 years.[11,12]

Tumor characteristics

Adenocarcinomas are characterized by their proliferative nature, typically manifesting as mucosal lesions. These tumors measure an average of around 4 cm, with recorded sizes ranging from 1.4 to 14.5 cm. The duodenum is the most frequent location for these tumors, accounting for 56% of cases, with the jejunum and ileum following in prevalence.[7,9,15,16]

Neuroendocrine tumors present as subepithelial lesions and are generally smaller, averaging 1.6 cm, with a range between 1.0 to 2.5 cm. These tumors are notable for their potential to produce serotonin, leading to carcinoid syndrome. The ileum is their most common site, constituting over 70% of cases, with occurrences also noted in the duodenum and jejunum.[7,9,15,16]

Gastrointestinal Stromal Tumors (GISTs), the most common neoplasm of mesenchymal origin, are primarily caused by gain-of-function mutations in the oncogenic KIT or PDGFRA tyrosine kinase enzymes. GISTs emerge from the interstitial cells of Cajal within the muscular layers of the small intestine's wall, presenting as subepithelial lesions. Their median size lies between 6 and 7 cm, with a broader range observed from 1.5 to 18.5 cm. GISTs are unique in that they can develop anywhere along the small intestine.[7,9,15,16]

Lymphomas, while also subepithelial in nature, frequently involve the mucosal layer and can lead to lymphangiectasia. These tumors typically measure 6.7 cm in median size, spanning from 1.7 to 20 cm. The ileum is the most common site for lymphomas, hosting 30% of cases, followed by occurrences in the jejunum and duodenum.[7,9,15,16]

Clinical presentations

The overall average age of small bowel tumor patients is between 50 – 60 years old. The diagnosis of tumors is slightly more common in men than women, which accounts for of 52-58%.[9,10,17,18] Common symptoms include abdominal pain (39-63%), palpable mass (8-28%), overt bleeding (12-44%), occult bleeding (14-37%), and weight loss (25-44%). Diarrhea is not common and has only been reported in 3-20% of cases. Complications such as acute abdominal conditions, ileus, and obstruction, have also been reported from 10-20% of cases. Different tumors have different common presentations. Table 2 summarizes the clinical presentations of each tumor type.[9,17]

As shown in Table 2, in small bowel adenocarcinoma the most common presenting symptom is abdominal pain, which accounts for approximately 40-76% of patients, followed by overt bleeding at 21-24% and occult bleeding at 12-38%.[9,17]

In NET, the patients can be asymptomatic, have prolonged vague abdominal symptoms, or present with complications of local tumor progression or distant metastasis. Some patients develop carcinoid syndrome, which typically develops in those with distant metastasis, especially liver metastasis, which is reported in 24% of patients. Carcinoid syndrome manifests as flushing (94%), diarrhea (78%), generally voluminous watery, and abdominal cramps (50%). Furthermore, some patients are prone to have valvular heart disease, which occurs in 50% of patients which is mainly due to a deposit of fibrous tissue at the heart valve.[9,14,17]

GISTs often present with various symptoms, including GI bleeding, abdominal pain, palpable masses, and weight loss. The most common presentation is gastrointestinal bleeding, which has been reported in up to 80% of cases, higher than other types of small intestine tumors.[9,17]

Lymphoma often presents with abdominal pain in 60-84% of cases. Additionally, it can present with acute abdomen, which is observed in up to 40% of cases. Acute abdomen is caused by bowel obstruction and peritonitis, each accounting for 20% of cases.[9,17]

In summary, all types of small bowel tumors present with abdominal pain 40-70% except for NET, which accounts for 27%. A palpable mass is mostly present in patients with GIST, accounting for 40-48%. Overt and occult bleeding is found predominantly in patients with GIST, accounting for 25-88%. Gut obstruction is mostly present in patients with adenocarcinoma and lymphoma.

Diagnosis

Computed tomography

In cases of adenocarcinoma, CT scan results often show irregular thickening of the wall in a small segment. Additionally, it may present as either an ulcerated lesion or a ring-shaped "apple core" lesion with a narrowing of the passage. After contrast administration, CT scans usually show heterogeneous density lesions and moderate enhancement, and they may contain vascular invasion or

TABLE 2. Clinical presentations separated by each tumor type.

	Adenocarcinoma	NET	Sarcoma (GIST)	Lymphoma
Age (mean, years)	63.2		54.4	55.6
Male	54		44	62
Presenting duration (median, month)	2 (3-14)		6 (1-120)	3 (1-36)
Abdominal pain	40-76%	27%	34-70%	60-84%
Palpable mass	0-28%	8%	11-56%	16-28%
Overt bleeding	21-24%	5%	40-48%	15-32%
Occult bleeding/anemia	12-38%	16%	25-88%	11-16%
Diarrhea	12%	38%	8%	20%
Acute abdomen	19-33%	8%	11-28%	40-44%
Obstruction	29%		1.4%	24%
Peritonitis	4%		9.6%	20%
Weight loss	28-77%	22%	23-32%	58-76%

Abbreviations: GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor

metastatic features, such as lymphadenopathy, peritoneal or distant metastasis.[19]

A typical CT finding in neuroendocrine tumors, formerly known as carcinoids, illustrates a single enhanced mass within the mucosa of the small intestine. Unlike adenocarcinoma, it is uncommon for NET to be ulcerated. Following contrast administration, CT scans commonly show arterial enhancement with washout in the portovenous phase. This pattern is similar to a mural mass with contrast enhancement extending into the nearby mesentery, resulting in the formation of a soft tissue density mass during later stages. If the mass involves mesentery, It may feature calcifications, often with spiky borders due to the desmoplastic reaction. This can induce fibrotic responses in nearby tissues, resulting in bowel obstruction, ischemia, or vascular compromise. NET typically produces metastasis to lymph nodes and the liver, which may lead to carcinoid syndrome.[19] The CT findings of NET are shown in Fig 2.

The CT characteristics of GISTs may differ based on tumor size and aggressiveness. Typically, they appear

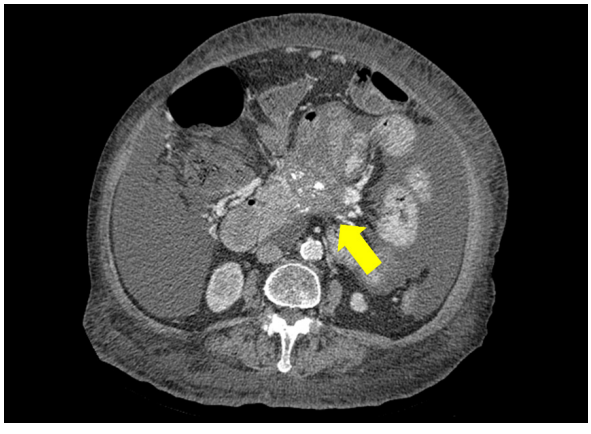

Fig 2. These features are typical of neuroendocrine tumors. A neuroendocrine tumor is characterized by a spiculated mass at the root of the mesentery with calcification and congestion of surrounding mesenteric vessels, which enhances in the post-contrast phase.

as large, prominently enhancing tumors visible on post-contrast imaging, although they may demonstrate hypo-enhancement and be situated within the lumen. GISTs typically exhibit significant enhancement during the arterial phase, followed by a decrease in enhancement during the venous phase. GISTs might display varied features because of necrosis or bleeding within the tumor and could lead to ulceration, formation of cavities, and connection with nearby structures through fistulas. Moreover, GISTs can induce obstruction in the small bowel either through direct pressure exerted by the mass or by causing the intestine to bend and compress. The bulky lymphadenopathy is uncommon in GISTs and is often found in other diagnoses rather than GISTs.[19] The CT findings of GISTs are shown in Fig 3.

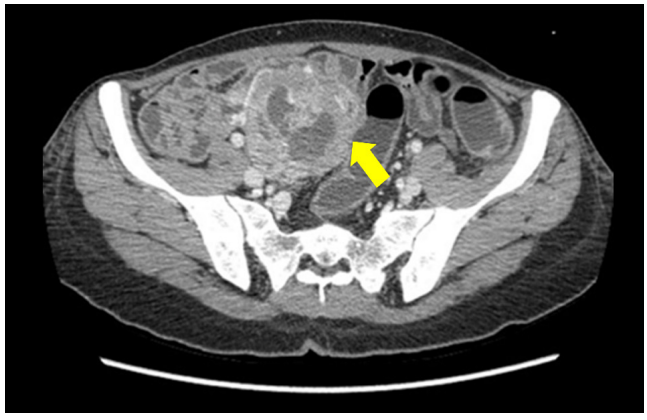

Fig 3. Computed topography in a 55-year-old female with gastrointestinal stromal tumor. The post-contrast phase of the CT scan reveals a large lobulated mass with internal necrosis, measuring 8.5x7.0 cm, located in the jejunoileal mesentery, abutting the walls of the jejunum and ileum.

The radiological presentation of lymphoma can vary significantly. In the initial stages, lymphoma might manifest as mucosal expansions resembling plaques. However, as the disease progresses, infiltrative lesions can lead to complete thickening of the wall and may even result in mucosal ulcers. Lymphomas are usually soft and preserve the lumen of the small intestine. Additionally, there may be dilation of the lumen (referred to as aneurysmal dilatation). Unlike adenocarcinoma, lymphomas can exhibit distinct CT scan characteristics, including prominent, uniform wall thickening (> 2 cm), eccentric stenosis, and concurrent lymph node enlargement. Additionally, they exhibit involvement at multiple sites compared to adenocarcinoma, often accompanied by distant lymph node enlargement and enlargement of the spleen. This can help distinguish lymphoma from other small bowel neoplasms.

In mesentery involvement, lymphoma does not incur vascular invasion compared with other types of small bowel tumors.[19]

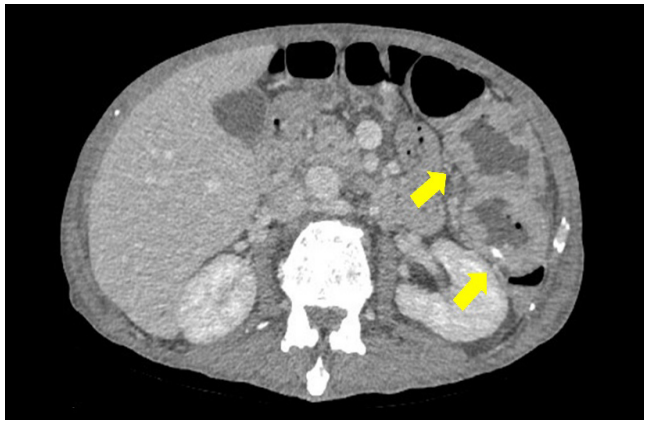

Fig 4. Small bowel lymphoma is demonstrated by marked asymmetrical bowel wall thickening with aneurysmal dilatation. However, it preserves the lumen of the intestine. Additionally, there are multiple lymphadenopathy. These features are typical of lymphoma.

Video capsule endoscopy

Video capsule endoscopy (VCE) can detect small bowel tumors in patients who have not had a tumor detected despite having undergone many investigations.[20,21] Fig 5 shows VCE findings of GIST. However, based on meta-analysis results comparing VCE to other diagnostic tools including push enteroscopy, small bowel follow through, and colonoscopy with ileoscopy, the VCE miss detection of neoplasms in 18.9% of all cases, which is higher than the miss rates of other lesions (4.7-8%).[22]

This is possible because of the unifocal nature of the tumor, and it is difficult to differentiate between a submucosal mass and an innocent bulge—a smooth protrusion of normal mucosa caused by loop bending or the pressure of an adjacent loop.[23] Compute tomography enterography can detect missed tumors by VCE[24], so the 2017 ASGE guidelines recommend performing CT enterography in patients with potential small bowel bleeding but negative VCE, or in patients suspected of having small bowel tumors.[25]

The endoscopic finding as described, Ulcerative masses were the most common morphological feature observed in lymphoma and adenocarcinoma cases, present in half of lymphoma patients (50%) and more than two-thirds of those with adenocarcinoma (72.2%). Additionally, a mucosal surface characterized by hyperemic nodularity was seen in 35% of lymphoma cases and 11.1% of adenocarcinoma cases. In patients with GIST, subepithelial tumors were the prevailing finding, occurring in nearly three-fifths of the cases (57.9%), while ulcerative masses were identified in over one-third of the cases (36.8%).[10]

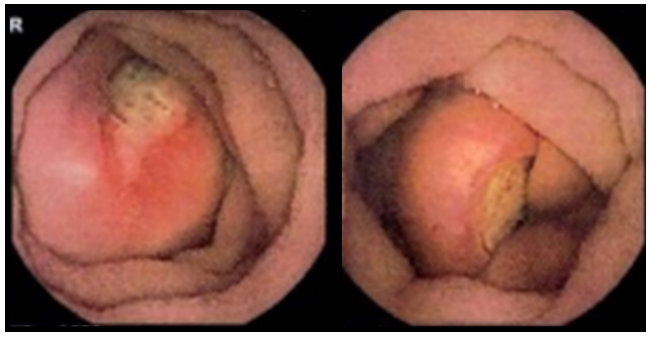

Fig 5. Imaging from video capsule endoscopy in a 55-year-old female with jejunal gastrointestinal stromal tumor shows an ulcerated subepithelial mass in the jejunum. The presence of an ulcerative lesion can be observed in over 30% of cases.

Radionuclide scan

Somatostatin receptor-based imaging can be useful for identifying NET. The first widely utilized functional imaging modality is somatostatin receptor scintigraphy or Octreoscan, which adopts 111 Indium pentetreotide uptake to visualize NETs. Somatostatin-receptor for functional PET imaging, using gallium Ga-68 DOTATATE (Ga-68 DOTATATE), gallium Ga-68 DOTATOC (Ga-68 DOTATOC), or gallium Ga-68 DOTANOC are approved in the US for usage in conjunction with integrated PET/CT for diagnostic imaging of NETs. These PET modalities can more sensitively detect NETs and have the potential to provide improved spatial resolution.[26]

Tumor markers

Tumor markers are helpful in the diagnosis of NET. The tumor is able to secrete both nonhormonal and hormonal tumor markers. 5-Hydroxyindoleacetic acid (5-HIAA) serves as a serotonin byproduct and is utilized as an indicator for serotonin levels. Conducting a 24-hour urine collection for 5-HIAA can confirm the presence of carcinoid syndrome. The test exhibits an overall sensitivity of 70% and specificity of 90% for diagnosing carcinoid syndrome. However, the accuracy of the results can be influenced by various drugs and food items, such as avocados, pineapples, bananas, kiwi fruit, walnuts, and pecans, which have been found to elevate urinary 5-HIAA levels. It's recommended to avoid consuming these items when undergoing testing for accurate results.[26-28]

Chromogranin A (CgA) is an acid glycoprotein with 439 amino acids present in most neuroendocrine cells' secretory dense core granules. It is acknowledged as a prevalent serum marker due to its secretion alongside the amines and peptides found in neurosecretory granules within tumors. Its sensitivity for accurately identifying the progression of well-differentiated gastroenteropancreatic NETs confirmed by imaging is modest, at 60%, while its specificity remains high at 90%.[26-28] Nevertheless, false-positive elevation of chromogranin can occur in certain conditions, such as chronic kidney disease, Parkinson's disease, untreated hypertension, pregnancy, steroid treatment or glucocorticoid excess, chronic atrophic gastritis or treatment with acid suppressant medications, especially Proton-pump inhibitors.[26,27]

Treatment

Adenocarcinoma

Surgery - Localized invasive adenocarcinomas of the small bowel can be best optimized by surgical resection. Furthermore, surgery can be performed in patients presenting with obstructive symptoms for palliative surgery.

Medical treatment – In metastatic disease, systemic chemotherapy is the mainstay of treatment in these settings. Several drugs have shown effectiveness in treating metastatic small bowel adenocarcinomas, such

as Capecitabine, 5-fluorouracil, Cisplatin, 5-fluorouracil, Gemcitabine, and Irinotecan, with varying response rates. An oxaliplatin-based chemotherapy regimen is considered to be a first-line regimen. The role of targeted therapy in expressing both VEGF with 91% and EGFR with 71% is highly illustrated in small bowel adenocarcinomas and KRAS mutations. Patients with genomic expression are considered for targeted agents such as bevacizumab, regorafenib, or anti-EGFR monoclonal antibodies.[29]

Nowaday, Immune checkpoint inhibitors, such as Pembrolizumab, which is a programmed death receptor 1 inhibitor (PD-1 inhibitor), play a role in the treatment of some metastatic small bowel adenocarcinomas with deficient mismatch repair (dMMR). Some studies have demonstrated the benefits of Pembrolizumab in the treatment of small bowel adenocarcinoma. In the United States, Pembrolizumab is approved for the treatment of various advanced solid tumors, including small bowel adenocarcinomas that exhibit microsatellite instability-high (MSI-H) or dMMR and have progressed after prior treatment. This approval represents a significant milestone as it is the first approval of a tissue-agnostic anticancer treatment when no satisfactory alternative treatment options are available.[30,31]

Neuroendocrine tumors

Surgery – Resection of the tumor is pragmatic for locoregional and resection of liver metastasis to improve overall survival.[14,26]

Medical treatment – In systemic therapy, somatostatin analogs are beneficial due to the high expression of somatostatin receptors in NETs. Activation of these receptors by synthetic somatostatin peptide mimetics helps inhibit cell proliferation pathways and decrease hormone secretion. Numerous clinical trials have shown that somatostatin analogs are highly effective as initial medical treatment, preventing tumor progression and managing symptoms of carcinoid syndrome in advanced gastroenteropancreatic NETs.[14,26] Everolimus actions by blocking the mammalian target of rapamycin (mTOR) protein, which activates a kinase downstream of the phosphoinositide 3-kinase/Akt pathway, supporting tumor cell survival, angiogenesis, and growth. Everolimus may play a role in additional treatments of small bowel neuroendocrine tumors.[14,26]

Gastrointesinal stromal tumor

Surgical resection is favorable for potentially resectable tumors.

Medical treatment – The treatment of Gastrointestinal Stromal Tumors (GISTs) underwent a significant transformation when it was discovered that mutations in the KIT or PDGFRA genes could activate the growth of these cancer cells. This discovery led to the development of effective systemic therapies in the form of small molecule inhibitors that target these receptor tyrosine kinases. Imatinib is an effective inhibitor when there is abnormal tyrosine kinase activity due to molecular rearrangements.

TABLE 3. Summary of treatment options for small bowel tumors.

	Surgery	Medical treatment
Adenocarcinoma	Resection Hepatic resection in liver metastasis	Oxaliplatin-containing regimen Fluoropyrimdine-base chemoradiotherapy VEGF-A inhibitor: bevacizumab EGFR inhibitor: cetuximab Immune checkpoint inhibitor
NET	Resection Radioembolization in liver metastasis	Somatostatin analogs mTOR inhibitor: everolimus, VEGF-A inhibitor: bevacizumab Interferon Cytotoxic therapy: poor response
Sarcoma (GIST)	Resection	Tyrosine kinase inhibitor
Lymphoma	Resection in cases with complications (obstruction/perforation)	Standard CMT for lymphoma

Abbreviations: GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor

Subsequently, it became clear that targeted therapy with imatinib provided remarkable, fast, and long-lasting clinical benefits in GISTs.

There is a trend in the use of TKIs for GISTs that do not respond well to initial treatment, particularly in advanced gastrointestinal stromal tumor patients. This includes medications like Sunitinib, which is approved in the United States for treating advanced GISTs that do not respond adequately to imatinib or are intolerant to it.[32-34]

Regorafenib, a multikinase inhibitor with activity against KIT, PDGFR, VEGFR, and others), is indicated for patients who do not respond to imatinib and sunitinib. Furthermore, Ripretinib is also approved by the US Food and Drug Administration (FDA) for advanced GIST patients who have previously received three or more TKIs, including imatinib.[32,35] However, some GIST patients, particularly those without KIT or PDGFRA mutations, do not experience significant benefits from initial TKI treatment with imatinib. Therefore, further research will be required in the future.

CONCLUSION

This review highlights the increasing incidence and complex heterogeneity of small bowel tumors (SBTs), which pose significant diagnostic and therapeutic challenges. Future research should focus on comprehensive epidemiological data to further understand the global burden of SBTs and the impact of environmental and genetic factors on their incidence. Furthermore, the development of biomarkers for early detection, longitudinal studies to elucidate the long-term efficacy of new treatment modalities, and the implementation of precision oncology to tailor therapies based on individual genetic profiles are warranted.

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Navigating the Nomenclature of Liver Steatosis: Transitioning from NAFLD to MAFLD and MASLD - Understanding Affinities and Differences

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ABSTRACT

The escalating prevalence of non-alcoholic fatty liver disease (NAFLD) represents a significant challenge to public health, with an increasing impact observed across various demographics. This review delivers a comprehensive evaluation of the evolving terminology in steatotic liver disease (SLD), documenting the transition from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD), and progressing to the latest terms, metabolic dysfunction-associated fatty liver disease (MASLD) and MASLD with increased alcohol intake (MetALD). We conducted a comprehensive review of literature discussing the benefits and drawbacks of these nomenclatural changes. Clinical evidence supporting MASLD and MetALD, including the implications of alcohol consumption thresholds on disease classification and outcomes, was analyzed. The "MAFLD" and "MASLD" labels align with the pathophysiology of metabolic diseases, afford a positive disease connotation, and facilitate the identification of more severe diseases, such as significant fibrosis or advanced liver disease. However, the MAFLD criteria may underdiagnose lean, non-overweight, or non-obese individuals with MAFLD. The review underscores the understanding of liver diseases linked to metabolic dysfunction and alcohol use. The shift in terminology marks progress towards a clinical diagnosis that reflects underlying pathophysiology. However, additional studies are necessary to assess the long-term effects of these changes and their efficacy in enhancing patient care and health outcomes.

Keywords: NAFLD; MAFLD; MASLD; MetALD; fatty liver (Siriraj Med J 2024; 76: 234-243)

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent condition affecting approximately one-quarter of individuals of the global population.[1-4] In a large prospective study in the US employing magnetic resonance imaging (MRI) and liver elastography, an estimated prevalence of NAFLD was 38%, with 14% categorized as non-alcoholic steatohepatitis (NASH).[5] Similarly, a pooled analysis among European countries revealed a 26.9% NAFLD prevalence,[6] whereas in Asia, the overall prevalence was approximately 30% which increased to 33.9% in 2017.[7] Notably, a predicted model anticipated a further 18.3% increase in the global prevalence, with China exhibiting the highest rise owing to its aging population and diabetes.[8] Moreover, the number of liver transplants due to hepatocellular carcinoma (HCC) from fatty liver without significant alcohol consumption between 2002 to 2012 increased by nearly 4-fold, becoming the third leading indication for liver transplantation in the US.[9] Given the enormous burden and rapid growth of NAFLD, prevention strategies and NASH therapy are imperative.[10] The spectrum of disease is heterogeneous;

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from simple steatosis, steatohepatitis, cirrhosis, and eventually HCC development, particularly in patients having advanced fibrosis and cirrhosis.[11] The majority of HCC in patients with NAFLD occurred in the cirrhotic background, however, a substantial proportion of up to 38% had arisen from non-cirrhosis.[12] Importantly, patients with fatty liver disease are at risk of developing not only hepatic but also extrahepatic cancers, including endometrial cancer, gastric cancer, pancreatic cancer, and colon cancer.[13]

In the past, fatty liver disease was classified into 2 groups: alcohol-associated liver disease (ALD) and NAFLD, based on the amount of alcohol consumption in individuals with evidence of hepatic steatosis.[14–19] In 2020, an international consensus proposed a new terminology, namely metabolic dysfunction-associated fatty liver disease (MAFLD).[20] This change carries potential benefits in increasing awareness and in accordance with pathophysiologic aspects, as metabolic dysfunction results in a wide range of systemic derangement, including liver disease. More recently, in June 2023, the new nomenclature with the overarching term of steatotic liver disease (SLD) comes with the new subclassifications of metabolic dysfunction-associated fatty liver disease (MASLD), MASLD with increased alcohol intake (MetALD), and ALD has been introduced and endorsed by the international liver societies.[21–23] This review focuses on the transition of nomenclature from NAFLD to MAFLD to MASLD/MetALD, and its impacts.

Naming change from NAFLD to MAFLD

In 2020, a group of international experts proposed a new nomenclature of NAFLD to MAFLD, using positive criteria (metabolic dysfunction) rather than a negative one (non-alcoholic), and did not exclude patients with significant alcohol consumption or concomitant with other chronic liver diseases.[20] Table 1 depicts the comparisons between NAFLD and MAFLD. The diagnostic criteria included evidence of hepatic steatosis along with one of the following: 1) overweight or obesity (≥23 kg/m^2 in Asians or ≥25 kg/m^2 in Caucasians), 2) diagnosis with type 2 diabetes, or 3) presence of at least 2 criteria of cardiometabolic and MAFLD risks. Metabolic risks from physical examination included the presence of an increase in waist circumference (WC: ≥90 cm or ≥80 cm in Asian men and women, respectively or ≥102 cm and ≥88 cm in Caucasian men and women, respectively), high blood pressure (≥130/85 mmHg) or use of antihypertensive drug.[20] Evidence of elevated triglycerides level (TG) (≥150 mg/dL), low level of HDL-cholesterol (<40 mg/dL in men or <50 mg/dL in women), prediabetes status (defined as fasting plasma glucose (FPG) levels 100-125 mg/dL or hemoglobin (Hb) A1c 5.7-6.4% or 2-hour post prandial plasma glucose levels 140-199 mg/dL), homeostasis model assessment of insulin resistance (HOMA-IR) score ≥2.5, high sensitivity C-reactive protein (CRP) level >2 mg/L were considered essential metabolic risk factors for the diagnostic criteria in individuals who are non-overweight/obese and absence of diabetes mellitus.[20]

TABLE 1. Comparisons between NAFLD and MAFLD.

Characteristics	NAFLD	MAFLD
Alcohol use	Exclude NAFLD if consume >3 drinks/day in men or >2 drinks/day in women	Can be included
Viral hepatitis	Exclude NAFLD if the presence of hepatitis B or hepatitis C	Can be included
Other chronic liver diseases	Exclude NAFLD	Can be included, such as drug-induced liver injury, autoimmune hepatitis
Cirrhosis	Mostly diagnosed with cryptogenic cirrhosis	Can be diagnosed with MAFLD-related cirrhosis if having evidence of steatosis in the past or present with risk factors of MAFLD
Alternative cause of fatty liver	Previously defined as a secondary cause	no more 'primary' or 'secondary' causes of fatty liver, only MAFLD and alternative causes of fatty liver

Reasons for the name change

While the term NAFLD has been widely used for a long-term, it appears to have certain significant drawbacks. NAFLD is a term with a negative connotation (non-) and can stigmatize those with alcohol use issues. Additionally, NAFLD fails to encapsulate the primary pathogenesis of the disease, which is metabolic derangement. Contrarily, the new term, MAFLD, provides greater mechanistic insight into metabolic dysregulation including inflammatory markers such as highly sensitive CRP, and uses the positive criteria to establish the diagnosis. Furthermore, other causes of chronic liver disease (CLD) need to be excluded in the diagnosis of NAFLD, while MAFLD, covers patients with dual liver pathology e.g., MAFLD with hepatitis C virus, MAFLD with autoimmune hepatitis, or when associated with ALD. Additionally, NAFLD studies often rely on histology for eligibility, potentially impeding trial endpoints. Using the term MAFLD and understanding its multiple phenotypes may be beneficial for clinical trial design and developing therapies targeted to different subtypes of MAFLD. Lastly, renaming NAFLD to MAFLD could improve public recognition and increase the chance of receiving funds, as it acknowledges that fatty liver can be associated with metabolic dysregulation rather than just liver disease alone.

Diagnosis of MAFLD with other etiologies

MAFLD can coexist with other CLDs, accelerating the progression of liver fibrosis and cancer development. The most common etiology that is associated with MAFLD is ALD.[24] In the presence of dual causes, the patients were more likely to be younger, with male sex preponderance, elevated liver enzymes, and higher Aspartate Aminotransferase (AST) to Platelet Ratio Index.[25] The positive criteria for the diagnosis of MAFLD reflect the real situation in clinical practice where many etiologies of CLD might coexist in a single patient. The NAFLD criteria allowed the alcohol intake with certain cutoff levels (<3 drinks/day in men and <2 drinks/day in women).[14–16] Currently, there is no longer a so-called 'safe amount' of alcohol intake.[26] A large database study that included 28 million individuals globally indicated that the level of alcohol consumption that can minimize the harm of alcohol is zero.[27] Similarly, a 4.9-year follow-up study of 58,927 Korean patients with NAFLD reported that light and moderate drinkers were also associated with worsening fibrosis scores.[28] Another study also supported alcohol abstinence to minimize the risk of fibrosis progression, particularly in patients with metabolic syndrome.[29]

However, MAFLD in combination with chronic hepatitis B (CHB) infection, still exhibited controversial results for the long-term outcomes when compared with those associated with CHB alone. The presence of hepatic steatohepatitis has been shown to be a strong predictor of having significant fibrosis (odds ratio [OR] 10.0, 95% confidence interval [CI], 2.08–48.5) and advanced fibrosis (OR 3.45, 95% CI, 1.11–10.7).[30] Hepatic steatosis was also significantly associated with a 4-fold increased risk of all-cause mortality and cancer.[31] Another long-term cohort study, including more than a thousand patients from 2 tertiary centers in Canada and Netherlands, demonstrated that 27.5% of patients with CHB were concomitant with MAFLD, and was proven histologically,[32] while those with MAFLD had an increased risk of decompensation (adjusted hazard ratio [HR] 2, 95% CI 1.26–3.19) and HCC (adjusted HR 1.93, 95%CI 1.17–3.21). Recently, a study from Rugivarodom et al, reported that patients with CHB with concomitant hepatic steatosis on liver biopsy were at a higher risk of developing liver-related mortality (HR 3.7).[33] Contradictorily, few studies also demonstrated that the liver-related complications were not statistically significantly different between patients with CHB with and without hepatic steatosis.[34]

Hepatitis C infection, particularly in genotype 3, is directly associated with causing hepatic steatosis.[35] Other genotypes were associated with steatosis via the mechanism of insulin resistance.[36] Overall, the prevalence of dual chronic hepatitis C (CHC) infection and fatty liver was approximately 27%-44.8%.[37,38] Concomitant hepatic steatosis and CHC accelerated fibrosis progression and extrahepatic events including cardiovascular, renal events and cancer development.[39,40]

In summary, a combination of other causes of CLD with MAFLD was generally associated with poor outcomes, as well as both hepatic and extrahepatic complications. Nonetheless, it has been concluded that virological suppression and sustained virological response in individuals with CHB and CHC can improve hepatic fat.[31,41]

Comparisons of NAFLD and MAFLD

Table 2 illustrates studies comparing NAFLD and MAFLD. The vast majority of patients with fatty liver can be included by either using the NAFLD or MAFLD criteria. Although some studies showed the same producibility and characteristics of patients in the diagnosis of fatty liver between NAFLD and MAFLD criteria[42–44], several others reported the advantages of MAFLD criteria over NAFLD, including enhanced detection of patients with significant or advanced hepatic fibrosis, cardiovascular risk,[25,32,45–50] as well as a higher all-cause mortality.[51] Interestingly, non-obese MAFLD may be overlooked due

TABLE 2. Summarized comparative studies between MAFLD and NAFLD.

Author, year	Sample size	Study design	Key results	Implication
Lin *et al.*[53], 2020	13,083	Retrospective study using data from the third National Health and Nutrition Examination Surveys of the United States, 1988-1994 (NHANES III)	MAFLD prevalence 31.24% NAFLD prevalence 33.23% Patients with MAFLD had higher age, higher body mass index, higher diabetes, hypertension, insulin resistance, hepatic enzymes, and liver fibrosis score (NFS score, FIB-4 score, and BARD score)	MAFLD criteria can better identify patients with advanced fibrosis when compared with the NAFLD criteria.
Wong *et al.*[42], 2020	1,013	Retrospective study from Hongkong census database, using MRI, liver stiffness measurement (FibroScan®)	MAFLD 25.9% NAFLD 25.7% NAFLD only 5.1% Only one with both MAFLD and NAFLD had FibroScan® ≥10 kPa.	MAFLD criteria did not show a significant change in NAFLD prevalence.
Yamamura *et al.*[45], 2020	765	Retrospective study in health check-up, Japan, using FIB-4, liver stiffness measurement	MAFLD 79.6% NAFLD 70.7% MAFLD (OR 4.401; 95% CI 2.144–10.629; p<0.0001), alcohol intake (OR 1.761; 95% CI 1.081–2.853; p=0.0234), and NAFLD (OR 1.721; 95%CI 1.009–2.951; p=0.0463) associated with F2 fibrosis.	MAFLD criteria could identify more patients with significant fibrosis.
Baratta *et al.*[52], 2021	795	Cohort study (The Plinio Study), Italy	96.5% of NAFLD identified with MAFLD MAFLD criteria missed 28 in 68 patients of lean NAFLD (41%).	Most NAFLD patients overlapped with MAFLD. However, a substantial lean NAFLD may be missed.
Ciardullo *et al.*[44], 2021		A cross-sectional study of NHANES, 2017-2018, using controlled attenuation parameter (CAP) and transient elastography	NAFLD 37.1% MAFLD 39.1% Similar risk of advanced fibrosis (7.5% vs. 7.4% among NAFLD and MAFLD, respectively)	The new MAFLD criteria had the same diagnostic yield when compared with that of the NAFLD criteria.

TABLE 2. Summarized comparative studies between MAFLD and NAFLD. (Continue)

Author, year	Sample size	Study design	Key results	Implication
Fujii *et al.*[47], 2021	2,254	A cross-sectional study in Japan, using FibroScan-aspartate aminotransferase (FAST) score to identify progressive liver disease.	MAFLD 35% NAFLD 27.4% MAFLD criteria had a higher FAST score (≥0.35) than did NAFLD criteria (8.6% vs. 7.7%).	MAFLD criteria may identify progressive liver disease by FAST score.
Guerreiro *et al.*[48], 2021	1,233	Retrospective study, biopsy-proven, 2013-2018, Brazil	MAFLD had numerically higher cardiovascular event incidences than did NAFLD (20.1% vs. 12.8%, p=0.137). MAFD with viral hepatitis had a higher 10-year cardiovascular risk than negative viral hepatitis MAFLD (21.1% vs. 4.3%, p=0.02)	MAFLD with other HBV+/- HCV infection had a higher 5-fold risk of cardiovascular event when compared with MAFLD associated with no viral hepatitis infection.
Huang *et al.*[46], 2021	175	Retrospective study, National Taiwan University Hospital, Taiwan	Both MAFLD and NAFLD 41.1% MAFLD 43.8% NAFLD only 4.9% MAFLD only 10.3% MAFLD only had high bilirubin levels, low platelet count, high NAS score, and advanced cirrhosis percentage (48.1% vs 0%, p<0.05).	MAFLD only without NAFLD had severe disease and severe histology than patients with NAFLD only.
Huang *et al.*[54], 2021	1,217	Retrospective study, Fujian Hospital, China, biopsy-proven	MAFLD 35% NAFLD 48.07% MALFD did not capture steatosis 13.8%.	MAFLD criteria may overlook steatosis.
Niriella *et al.*[49], 2021	2,985	Retrospective study, community-based cohort in Sri Lanka	MAFLD 33.1% NAFLD 31.5% In patients with MAFLD but not NAFLD (2.9%) had higher odds of developing incident general obesity, central obesity, diabetes, and cardiovascular events.	Patients with MAFLD have high risks for metabolic and cardiovascular events.

TABLE 2. Summarized comparative studies between MAFLD and NAFLD. (Continue)

Author, year	Sample size	Study design	Key results	Implication
Tsutsumi *et al.*[50], 2021	2,306	Cohort study, Japan	MAFLD 80.7% NAFLD 63.4% MAFLD (HR 1.08, 95% CI 1.02–1.15, *p*=0.014) and alcohol consumption (20–39 g/day; HR 1.73, 95% CI 1.26–2.36, *p*=0.001) were independently associated with worsening of the Suita score.	MAFLD criteria better identified patients with a higher risk of cardiovascular disease.
Van kleef *et al.*[55], 2021	5,445	A cross-sectional analysis within the Rotterdam Study (large prospective population-based cohort), ultrasound-based	MAFLD 34.3% NAFLD 29.5% MAFLD only 5.9% NAFLD only 1% MAFLD only was strongly associated with fibrosis (adjusted OR 5.3).	MAFLD criteria improved the detection of fibrosis.
Zhang *et al.*[43], 2021	19,617	Retrospective study from NHANES,1999-2016	MAFLD increased from 28.4% to 35.8% and was higher than NAFLD (33%). MAFLD and NAFLD had similar 10-year cardiovascular risk (13.2% vs. 12.9%) and chronic kidney disease (18.7% vs. 18.8%).	MAFLD had the same cardiovascular and renal dysfunction compared with NAFLD.
Kim *et al.*[51], 2021	7,761	Participants in the NHANES III with linked mortality data	Prevalence of any fatty liver was 32.6% -23.5% concordant between NAFLD and MAFLD -6.1% NAFLD only -2.4% MAFLD only Hazard ratio (HR) for all-cause mortality: -MAFLD+/NAFLD+ 1.26 (95%CI: 1.16-1.38) -MAFLD-/NAFLD+ 0.90 (95%CI: 0.56-1.43) -MAFLD+/NAFLD- 1.97 (95%CI: 1.47-2.64)	MAFLD was significantly associated with increased mortality while NAFLD without metabolic risk factors was not.

Abbreviations: ALD, alcoholic associated liver disease; CAP, controlled attenuation parameter; FAST, FibroScan-aspartate aminotransferase score; FIB-4, Fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NAS score, non-alcoholic fatty liver disease activity score; NFS, NAFLD fibrosis score; NHANES III, the third National Health and Nutrition Examination Surveys of the United States

to the absence of any obvious metabolic dysregulation under the new criteria.[52] This drawback might stem from the lack of inflammatory or insulin resistance markers in retrospective studies, which are now incorporated in the new MAFLD criteria if the patients are non-obese or non-diabetic.

Most recent nomenclature: MASLD and MetALD

More recently, in June 2023, the newest nomenclature of the MASLD under the overarching term of SLD, was introduced in the International Liver Congress held in Vienna. This nomenclature was derived from the Delphi consensus process and endorsed by the major hepatology societies.[21–23] In this updated nomenclature, not only is the term "MASLD" introduced, but for the first time, another unique category of MetALD was established.

In the transition from NAFLD to MAFLD, the authors proposed replacing the term "nonalcoholic" with "metabolic dysfunction" to better reflect the etiology of the disease rather than merely excluding significant alcohol consumption in patients with hepatic steatosis. However, the term "fatty" in MAFLD is considerably stigmatizing for the patients, whereas "steatotic" in MASLD is more neutral and medically inclined.[21–23] The term "steatotic" may cause confusion for patients regarding the disease due to its medical nature. Nevertheless, the impact of potentially stigmatizing terms in non-English speaking countries, such as Thailand, where both "fatty" and "steatotic" translate to the same word in Thai, remains unknown, potentially leading to uniform communication regarding the nomenclature of the disease between doctors and patients.

Furthermore, beyond the distinction between "fatty" and "steatotic", there are differences in the diagnostic criteria for MAFLD and MASLD.[20–23] The variations in the definitions of MAFLD and MASLD are depicted in Table 3. The most significant differences are the alcohol threshold and the number of cardiometabolic risks required for the diagnosis under each terminology. While MAFLD emphasizes the number of cardiometabolic risks and categorizes patients into obese, lean/normal weight, and type 2 diabetes MAFLD, the diagnosis of MASLD mandates the exclusion of significant alcohol consumption. For MASLD, if patients exhibit both cardiometabolic risk(s) and alcohol consumption >20/30 gm in women/men but less than 50/60 gm/day in women/men, they would be categorized as MetALD, and if the alcohol consumption exceeds 50/60 gm/day in women/men, regardless of cardiometabolic risk presence, they would be categorized as ALD.

Clinical evidence of the MASLD and MetALD nomenclature

Given that the alcohol intake threshold for diagnosing MASLD is the same as the previous criterion for diagnosing NAFLD, a clinical question arises regarding the potential utilization of existing NAFLD data under the new MASLD definition. Recent studies conducted in the US, Korea, and Hong Kong have demonstrated that the characteristics of individual patients with NAFLD and MASLD are nearly identical, with an overlap of up to 98% to 99% of patients.[56–58] Therefore, in general, the term MASLD can be used interchangeably with the previous term NAFLD. A study from India reported that the MASLD criteria is superior to MAFLD in diagnosing the disease in patients with normal weight/lean. Nevertheless, the major caveat is that this study was retrospective, and the HOMA-IR and the hs-CRP were unavailable for the majority of patients in that cohort.[59] The data regarding the comparisons between the MAFLD and MASLD criteria in both patients' characteristics and longitudinal outcomes are very limited, at this point.

MetALD, introduced for the first time, has its own definition due to concerns regarding the potential impact of varying alcohol intake on clinical outcomes in patients with cardiometabolic risk and the presence of hepatic steatosis. For instance, in patients with type 2 diabetes and fatty liver, it is unclear whether no/minimal alcohol intake or consuming moderate amounts would have different effects. The usefulness of determining this MetALD subcategory is yet to be explored. Some studies have indicated a higher risk of long-term overall and cardiovascular mortality in individuals with MASLD and MetALD compared to those without SLD.[57,60] However, specifical comparisons between MASLD and MetALD groups to assess the effect of alcohol consumption in patients with cardiometabolic features, using the same dataset of NHANES III dataset, have yielded a non-significantly higher risk of long-term overall mortality compared to the MASLD group at an adjusted hazard ratio of 1.11 (95%CI: 0.90-1.38, p=0.337), after adjusting the age, sex, smoking status, race-ethnicity, and liver fibrosis category level using a noninvasive biomarker. [unpublished data, the results of our analysis were presented at the EASL SLD summit in September 2023.]

Lastly, there are some challenges associated with the transition from the nomenclature NAFLD to MAFLD and MASLD. First, these terms may confuse patients because there are two terms, MAFLD and MASLD. Second, it is unclear whether the clinical trial endpoints for new drugs are the same for or differ between these two terms. Lastly, there is inconsistency in the adoption of the new term

TABLE 3. The differences in the definitions of MAFLD and MASLD.

Domain	MAFLD	MASLD
Identification of hepatic steatosis	Either imaging techniques, blood biomarkers/scores, or liver histology	Imaging or histology
Alcohol consumption	At any level can be included	<20/30 gm/day in women/men
Cardiometabolic risk	If the presence of obesity or type 2 diabetes ➜ MAFLD **If no DM and normal weight ➜ need ≥2 of the following to diagnose:** 1) WC ≥102/88 cm in men/women (≥90/80 in Asians). 2) Prediabetes (HbA1c of 5.7−6.4%, or FPG of 5.6–6.9 mmol/L, or 2-hour post-load glucose levels of 7.8−11.0 mmol/L). 3) Blood pressure ≥130/85 mmHg or under anti-hypertension therapy. 4) HDL-c <1.0/1.3 mmol/L for men/women. 5) TG ≥1.70 mmol/L or specific drug treatment. 6) HOMA-IR score ≥2.5. 7) hs-CRP level >2 mg/L.	≥1 of 5 cardiometabolic risk factors: 1) BMI ≥ 25 kg/m^2 [23 Asia] or 94 cm (M) 80 cm (F) or ethnicity adjusted 2) FPG ≥ 5.6 mmol/L [100 mg/dL] or 2-hour post-load glucose levels ≥ 7.8 mmol/L or HbA1c ≥ 5.7% [39 mmol/L] or type 2 diabetes or treatment for type 2 diabetes 3) Blood pressure ≥ 130/85 mmHg or specific antihypertensive drug treatment 4) TG ≥ 1.70 mmol/L [150 mg/dL] or lipid lowering treatment 5) HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) or lipid lowering treatment
Subtypes	1. obese MAFLD 2. lean/normal weight MAFLD 3. type 2 diabetes MAFLD	None, but those with alcohol consumption between 20/30 and 50/60 gm/d in women/men were categorized into MetALD.

by international liver societies; for example, MASLD is endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), whereas MAFLD is endorsed by the Asian Pacific Association for the Study of the Liver (APASL).

CONCLUSION

In conclusion, efforts to improve disease nomenclature based on the underlying pathophysiology, as well as raising awareness among doctors, patients, and the public awareness on fatty liver disease, have been made substantial in recent years. Emphasizing the role of metabolic dysfunction as a cause of disease and acknowledging its significant long-term cardiometabolic morbidity and mortality risk is crucial. Nonetheless, further investigation is necessary to determine whether the MASLD and MetALD definitions offer superior diagnostic and prognostic value compared to the MAFLD definition.

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Conflict of interest

Kaewdech A. and Sripongpun P. declare no conflicts of interest.

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