Editorial

Is there a role for percutaneous needle aspiration in the multimodal management of pyogenic liver abscess?

Kai Siang Chan[1]^, Martin Weng Chin H'ng[2], Vishal G. Shelat[1]^

[1]Department of General Surgery, Tan Tock Seng Hospital, Singapore, Singapore; [2]Department of Radiology, Tan Tock Seng Hospital, Singapore, Singapore

Correspondence to: Kai Siang Chan, MBBS. Department of General Surgery, Tan Tock Seng Hospital, Singapore 308433, Singapore. Email: kchan023@e.ntu.edu.sg.

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Liver abscess is defined as a pus-filled mass in the liver and may be classified as pyogenic, amoebic, parasitic (other types of parasite) or fungal. Pyogenic liver abscess (PLA) and amoebic liver abscess (ALA) remain the most common types of liver abscesses. Common causative organisms for PLA are *Klebsiella pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus* (1), while ALA is caused by extra-intestinal dissemination of *Entamoeba histolytica*. Incidence of PLA and ALA varies between the Eastern and Western populations (2), but nevertheless, both are reported to cause a mortality risk of 10–30% (1).

With technological advancements, percutaneous interventions (aspiration or drainage) have largely replaced invasive surgical drainage and remain the main choice of source control for PLA >4 cm or failure of conservative management with medical therapy (3). We have reported good clinical outcomes in patients with PLA following implementation of a liver abscess care bundle (integration of surgical, interventional radiology, infectious disease and nursing teams) (4). In 2015, Cai *et al.* (5) performed a meta-analysis on 5 randomized controlled trials (RCTs) including 306 patients and showed superior success rate of percutaneous catheter drainage (PCD) compared to percutaneous needle aspiration (PNA). However, their study was limited by the small sample size and heterogenous population (2 studies with PLA only, and 3 studies with mix of ALA and PLA). Thus, the recent meta-analysis performed by Mahmoud *et al.* is a timely update to the evidence regarding the use of PCD versus PNA (6).

Mahmoud *et al.* performed a meta-analysis on 15 RCTs with 1,626 patients (PCD n=824; PNA n=802) with liver abscess (6). Their main finding was that PCD was associated with higher success rate [n=13 studies; risk ratio (RR): 1.21; 95% confidence interval (CI): 1.10, 1.31; P<0.001] and lower recurrence after six months (n=8 studies; RR: 0.41; 95% CI: 0.22, 0.79; P=0.007). PCD was also associated with a shorter time to clinical improvement [mean difference (MD): −1.78 days; 95% CI: −2.50, −1.06; P<0.001], shorter time to achieve 50% reduction in abscess size (MD: −2.83 days; 95% CI: −3.36, −2.30; P<0.001) and shorter parenteral antibiotic duration (MD: −2.13 days; 95% CI: −3.84, −0.42; P=0.01) with comparable procedure-related adverse event rate (n=6 studies; RR: 2.20; 95% CI: 0.51, 9.54; P=0.29). As studies on both PLA and ALA were included, the authors performed a subgroup analysis; subgroups which included both PLA and ALA showed superior success rate with PCD, but not for the PLA only subgroup. This editorial shall discuss about the management of PLA and the utility of PCD and PNA in light of new evidence. We shall mention ALA where relevant, but the predominant emphasis will be on PLA due to different etiopathologies.

^ ORCID: Kai Siang Chan, 0000-0001-9533-801X; Vishal G. Shelat, 0000-0003-3988-8142.

The etiology of liver abscess (PLA *vs.* ALA) has an impact on management and clinical outcomes. While PLA and ALA are the most common types of liver abscesses, they have distinct etiopathology, clinical profile and management. Risk factors for PLA include older age, history of diabetes mellitus, underlying biliary disease, malignancy and liver transplantation (7). ALA on the other hand, is more common in younger and immunosuppressed patients, and usually occurs in temperate regions with poor sanitation (8). As the etiology of PLA and ALA is different, medical therapy similarly differs. Choice of antibiotics for PLA is largely guided by local antibiotogram and blood and/or fluid culture sensitivity results. For ALA however, metronidazole remains the mainstay treatment with good clinical response (9). Duration of antibiotics depends on clinical response to therapy and type of liver abscess; for PLA, studies have reported use of parenteral antibiotics for 1–3 weeks (10,11), with transition to oral antibiotics subsequently. In contrary, duration of antibiotics lasts about one week for ALA (9). While the overall success rate was higher in PCD compared to PNA, it is important to note that majority of included RCTs (n=11/15) had a mix of PLA and ALA. To add on, incidence of ALA ranged between 9.9% to 77% for studies which included a mix of ALA and PLA. Overall heterogeneity of all included studies was high (I^2=79%). Subgroup analysis is important to eliminate potential sources of heterogeneity. However, while subgroup analysis did not show any significant differences between PLA-only subgroup and PLA + ALA subgroup, both subgroups still had high heterogeneity. In addition, the PLA-only subgroup failed to show any significant improvement in success rate with PCD compared to PNA, though this is likely due to the small sample size (n=3 studies; 212 patients; RR: 1.28; 95% CI: 0.84, 1.96; P=0.25). While the design of RCTs helps to ensure comparable demographics to reduce confounding factors, difference in natural history between PLA and ALA may limit interpretation of results from the meta-analysis by Mahmoud *et al.* (6). This calls for a need for RCTs to evaluate the clinical outcomes of PLA only or ALA only.

The demographics and microbiology are important confounding factors for clinical outcomes. A recent meta-analysis by Chan *et al.* showed that *Klebsiella pneumoniae* PLA (KPPLA) was associated with lower mortality, but higher metastatic complications compared to non-KPPLA (12). *Klebsiella pneumoniae* has been shown to have unique virulent characteristics, such as presence of hypermucoviscosity phenotypes in K1 and K2 capsular serotypes (11). These hypervirulent characteristics may predispose patients to disseminated metastatic infections. However, their meta-analysis similarly showed that KPPLA occurred more frequently in younger patients without underlying hepatobiliary disease or malignancy; this group of patients may have improved physiological reserves resulting in better clinical outcomes. We have reinforced this hypothesis in a propensity score-matched study (13) including 102 patients with PLA and shown that elderly patients (≥65 years) had significantly longer length of stay compared to non-elderly patients (<65 years), though in-hospital mortality and incidence of PCD were similar. Of the 15 RCTs included by Mahmoud *et al.* (6), majority of the studies (66.7%, n=10/15) did not report on co-morbidities. These may confound the success rates in PCD *vs.* PNA. Existing studies have shown that underlying hypertension, hyperbilirubinemia, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, and Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥15 predict failure of PCD (14). In addition, co-morbidity is shown to impact clinical outcomes in patients with acute cholecystitis (15), acute cholangitis (16), and acute pancreatitis (17). Future studies should assess the impact of co-morbidities on liver abscess prognosis.

The radiological characteristics (e.g., multiple abscess, multi-loculation and size) are highly relevant in the choice between PCD and PNA. Multiple abscesses have been shown to be an independent predictor for failure of PCD (18). Incidence of solitary *vs.* multiple abscesses was comparable between the PCD and PNA groups in the included RCTs by Mahmoud *et al.* (6). However, the authors were unable to perform subgroup analysis for multiple abscesses as the individual RCTs did not compare the outcomes between PCD and PNA for multiple abscesses only. A benefit of PNA is its ability to aspirate multiple small abscesses in a single session (19). Undertaking repeated PNA for a large multi-loculated abscess has been broached in the article. This is traumatic for the patient and stretches hospital resources. In PCD, a needle and tube are inserted traversing and disrupting several internal locules, which is akin to repeating PNAs. In cases of repeated PNA, PCD may be a feasible alternative. However, performing PCD for multiple abscesses may result in more patient discomfort and risk of superficial skin infection due to presence of multiple drains *in-situ*. Drain insertion also impairs patients' quality of life and require caregiver training to patients and their caregivers for outpatient management. Being "connected" to a drainage bottle may limit mobility (which

comes with its own set of attending complications), and in the setting of regular bed turning or an uncooperative patient, this risks tube dislodgement. However, there are unique scenarios where PNA can be an adjunct to PCD, as in the case of (I) two nearby abscesses allowing PNA to be performed for one before proceeding with PCD for the other or (II) two adjacent abscesses permitting "skewering" and aspiration of one before deploying the drain in the dominant one. Clinicians are also faced with a dilemma on the optimal timing for drain removal. Based on our experience, the drain is left *in-situ* for a few weeks to allow for fibrosis and avoiding re-accumulation, and removed after repeat imaging shows near-complete resolution of the abscess. Tubogram has been reserved in selected cases where there is no improvement and a biliary communication is suspected. This burden is reversed in the context of PNA, where clinicians are faced with the decision on need and timing for repeat PNA.

There is no consensus defining the size cut-off limit for PCD/PNA. Studies have proposed various cut-offs ranging from 3–5 cm (4); we used the mathematical principles of a sphere and deduced that PLA >4 cm should undergo PCD/PNA. Cut-off values for liver abscess in the included RCTs ranged from 2–10 cm (6). Higher success rate in PCD may be due to larger catheter size (compared to needle) and availability of a continuous negative pressure drainage system in PCD. Included RCTs used catheter sizes ranging from 8 Fr (inner diameter 2.67 mm) to 14 Fr (inner diameter 4.67 mm) for PCD, and needle size ranging from 18 G (inner diameter 0.84 mm) to 16 G (inner diameter 1.19 mm) for PNA. When subgroup analysis was performed based on size of catheter, only studies which used 12 or 14 Fr catheters had superior success rate (RR: 0.17 and 0.08 respectively) compared to PNA, but not for 8 Fr catheter. This implies that catheters with larger diameters allow for better drainage and source control. However, larger catheters may result in more patient discomfort or cellulitis at puncture site. The meta-analysis by Mahmoud *et al.* showed comparable procedure-related adverse events between PCD and PNA (n=6 studies; RR: 2.20; 95% CI: 0.51, 9.54; P=0.29) (6). The lack of statistical significance may be due to the small sample size and low incidence of events [PCD: n=5/218 (2.3%); PNA: n=2/216 (0.9%)]. However, even with a significant difference between PCD and PNA, this may not be clinically significant (absolute difference in incidence is 1.4%). Future studies should assess quality of life and caregiver outcomes in PLA patients treated by PCD compared to PNA.

Following PCD/PNA, there may be abscess re-accumulation due to ongoing inflammation, inadequate drainage, or biliary communication. Placement of a catheter and negative pressure drain allows for continuous source control and prevents re-accumulation of pus. However, meta-regression analysis based on abscess size showed significant decrease in success rate with increasing abscess size (b=–0.0343, SE =0.0091, P=0.0002) (6). Is there is an upper limit for size cut-off in deciding whether surgical drainage (SD) should be attempted first-line? Traditionally, SD is reserved for PLAs refractory to medical therapy, presence of multi-loculation or giant PLA (≥10 cm) (3). Retrospective studies have shown higher resolution rates and reduced need for secondary procedure when SD is performed for PLA >5 cm (20). However, Ahmed *et al.* demonstrated the feasibility and safety of PCD in 39 patients with PLA ≥10 cm, with 92.3% success rate (without need for secondary intervention) and 25% overall morbidity (21). Additionally, with decrease in success rate of PCD with increasing abscess size, should PNA even considered if it has lower success rate compared to PCD? Based on existing evidence above, it is our informed opinion that PCD should be first-line drainage procedure for PLAs >4 cm.

There are three issues that we would like to raise regarding the meta-analysis by Mahmoud *et al.* (6). Firstly, the outcome on six-month recurrence. Six-month recurrence is not a commonly used outcome metric for PLA, and the definition of "recurrence" is varied and has room for clarification. For example, if a patient diagnosed with PLA is clinically well following source control and etiology treatment (e.g., cholecystectomy), a follow-up is unwarranted at six-month. Also, if interval imaging is performed at six-month follow-up, and the imaging shows residual features of a PLA, would that be considered as recurrence or persistence or even simply footprints of previous infection in an otherwise well patient? In our opinion, recurrence and persistence of PLA are important distinctions especially in patients treated by PNA and antibiotics alone, and six-month recurrence is not an evidence-based variable to be reported in context of PLA. It is likely that PNA patients would require longer duration of antimicrobial therapy to achieve clinical and radiological treatment response, and this brings us to the second issue. The longer duration of antibiotics therapy in PNA patients is concerning to us as it encourages antimicrobial resistance without any additional benefit of reduced length of stay (6). The impact of alternation of normal microbial flora and its

medium to long term consequences are unreported in any studies on liver abscesses; thus, clinicians must be mindful in interpreting the results of this study and its application in clinical care. Thirdly, if PCD is superior to PNA for source control without added morbidity, is there a role for PNA in the management of liver abscess? It appears that PNA might have a role in small liver abscess where microbial isolation is the predominant aim, allowing for culture-directed antibiotic administration, or as an adjunct to PCD in the appropriate setting. Initial resuscitation of liver abscess involves administration of broad-spectrum antibiotics which is tailored based on microbiology. A retrospective study on 528 patients with PLA showed that fewer patients with culture-negative PLA underwent PCD compared to KPPLA (34.8% *vs.* 63.6%, P=0.001) (22). This is an important finding as positive cultures could be due to bacteremia or due to microbial isolation from abscess fluid. As blood cultures are only positive in less than half of PLA patients and not all patients receive PCD (3,13,16,22), some patients will not have microbial isolation. While outcomes of empiric antibiotic therapy are not inferior in culture-negative patients (2,22), PNA remains attractive as a low-risk procedure to guide culture-directed therapy with possibility to reduce antimicrobial resistance. This is especially important with emergence of carbapenem-resistant Enterobacteriaceae infections (23). However, the role of PNA for therapeutic purposes needs to be defined and more evidence is necessary to select the ideal patients for therapeutic PNA. It is likely that abscess morphology, patient co-morbidities, local healthcare system capabilities, and patient-physician shared decision making are essential ingredients to define the role of PNA in the PLA treatment algorithm.

In conclusion, the meta-analysis by Mahmoud *et al.* summarized the evidence regarding the use of PCD versus PNA in liver abscess (6). Unlike PNA, PCD provides continuous drainage, which is key for source control. However, due to the small number patients with only PLA, the authors were not able to demonstrate superior of success rate of PCD compared to PNA. PLA of >4 cm should still be treated by antibiotics and PCD. PNA should be reserved for microbial isolation to guide culture-directed antibiotic therapy. PNA may be considered in low resource settings where cost and technical expertise are of concern, or when there are multiple smaller abscesses. Clinicians should refrain from choosing PNA solely because it causes less discomfort. Similarly, SD remains the last-line treatment not merely because it is more invasive, but also because PCD provides effective source control for liver abscess.

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Footnote

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