Original Article

Liver Masses: Radiological, Histopathological, and Immunohistochemical Correlation - A Retrospective Tertiary Care Hospital-Based Study

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Abstract

Background: Hepatic lesions consist of a wide range of abnormalities, including benign tumors, abscesses, primary malignancies, and metastatic tumors, each with distinctive histopathological and radiological findings. It is often challenging to differentially diagnose most metastatic lesions and some liver primaries based on clinical, radiological, and histopathological findings alone. Immunohistochemistry plays a crucial role in accurately diagnosing such lesions, which further aids clinicians in formulating an appropriate treatment plan.

Materials and Methods: The present cross-sectional retrospective study was conducted in the Department of Pathology at the American International Institute of Medical Sciences, Udaipur. Data from ultrasound-guided liver biopsies received in the department between January 2022 and October 2023 were collected. Immunohistochemical data for the respective cases were also gathered. Statistical analysis was performed using MedCalc software. A p-value of <0.05 was considered the cutoff for statistical significance..

Results: A total of 82 cases were included in the study. The mean age was 58.37 years. Of the 82 cases, 80 (97.5%) were malignant, and 2 (2.5%) were benign. Among the 80 malignant lesions, 10 (12.5%) were primary hepatic tumors, while 70 (87.5%) were metastatic tumors. Sensitivity, specificity, negative predictive value, positive predictive value, and diagnostic accuracy were 50.00%, 100.00%, 98.77%, 100.00%, and 98.78%, respectively. The p-value was statistically significant ($p < 0.024$).

Conclusion: Despite various advancements in imaging techniques, histopathological assessment followed by immunohistochemistry remains the gold standard for accurately diagnosing liver lesions. The integration and correlation of both radiological and pathological findings will provide better diagnostic accuracy, leading to improved patient care, prognosis, and overall survival.

Keywords:

Neoplasm, Radiology, Histopathology, Immunohistochemistry, Hepatocellular carcinoma, Metastasis.

Introduction

Hepatic lesions consist of a wide range of lesions, including benign tumors, cystic lesions, hepatic abscesses, primary malignancies, and metastatic tumors, which show distinctive histopathological and radiological findings [1,2]. According to the GLOBOCAN data 2020, primary liver cancers are the sixth most commonly diagnosed cancers worldwide and the third leading

cause of cancer-related deaths, with approximately 830,000 deaths and 906,000 new cases [3]. The incidence and mortality are two to three times higher in males than females in most regions, and it ranks second in terms of mortality in males [3]. The primary liver cancers include hepatocellular carcinoma, which comprises 75-85% of all cases, occurring against the background of chronic liver disease and liver cirrhosis, followed by intrahepatic cholangiocarcinoma, comprising 10-15% of cases, as well as other rare types [4,5]. Hepatic metastasis accounts for about 25% of all solid organ metastases and is far more common than primary hepatic tumors [6].

Metastases to the liver are mostly from carcinomas of the lung, pancreas, colon, stomach, and breast. The most common tumor type reported is adenocarcinoma, followed by neuroendocrine tumors. Other tumors frequently metastasizing to the liver include lymphomas, malignant melanoma, and, rarely, sarcomas [6]. It is very difficult to differentially diagnose most metastatic lesions and some liver primaries based on clinical, radiological, and histopathological findings alone. In such cases, immunohistochemistry plays a crucial role in making an accurate diagnosis and forming a proper treatment plan. Establishing the tumor type—whether it is a carcinoma, sarcoma, melanoma, neuroendocrine tumor, or lymphoma—is usually the first step [6]. Pathologists may have difficulties in differentiating between metastatic and primary hepatic neoplasms or in identifying the exact tumor type only on the routine hematoxylin and eosin (H&E) stained sections.

At times, it becomes impossible to differentiate metastatic adenocarcinoma from cholangiocarcinoma and hepatocellular carcinoma from metastatic lesions showing similar morphologies [6]. Hence, a combination of both morphological evaluation of H&E stained sections and immunohistochemistry is usually the standard practice for a prompt diagnosis. A multidisciplinary approach using the available clinical information and radiological findings, with careful selection of appropriate immunohistochemical markers, is essential in cases of unknown primary for definite tumor typing [6,7]. In recent times, various immunohistochemical markers are being used for decision-making in molecularly targeted therapies and also as predictive markers to assess the therapeutic response [4].

In the present study, we correlated the radiological findings with the histopathological and immunohistochemical findings of various liver masses.

Materials and Methods

The present study is a cross-sectional retrospective analysis conducted in the histopathology section of the pathology department at the American International Institute of Medical Sciences, Udaipur, Rajasthan, a tertiary healthcare center. The study was ethically approved by the institutional ethical committee (Reference number: IEC/Research/2024/52). Data from ultrasound-guided biopsies of liver lesions received in the department from January 2022 to October 2023 were collected. The biopsies were received in 10% neutral buffered formalin. After adequate fixation, they were submitted for routine processing, followed by paraffin embedding and staining with Hematoxylin and Eosin. Clinical history, serum tumor marker levels, imaging findings, and other relevant data of the patients were extracted from laboratory requisition forms received from the clinicians. The blocks were then outsourced for immunohistochemical staining using appropriate markers, and the immunohistochemical data of the respective cases were also collected. A final diagnosis was made after correlating the radiological, histopathological, and immunohistochemical findings. All patients with liver lesions were included in the study.

Statistical analysis: The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the data were analyzed using MedCalc software, and a p-value of <0.05 was considered the cutoff value for significance.

Results

A total of 82 cases were included in the study, of which 47 (57.3%) were males and 35 (42.6%) were females. Most of the patients were in the age group of 61 to 70 years. The mean age was 58.37 years. Out of the 82 cases, 80 (97.5%) were malignant, and 2 (2.5%) were benign lesions. Of the 80 malignant lesions, 10 (12.5%) were primary hepatic tumors, while 70 (87.5%) were metastatic tumors [Fig. 1].

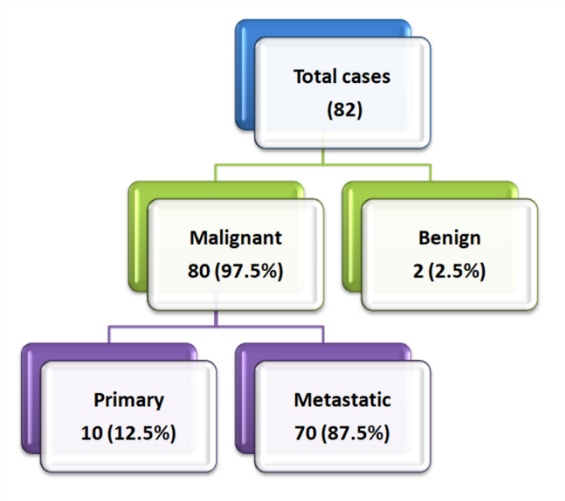

Figure 1: Flow chart classifying the liver biopsy cases

Based on radiological findings, including contrast-enhanced computed tomography and ultrasonography of the whole abdomen, 1 (1.2%) case had a benign lesion—a hydatid cyst. Seventy-nine (96.4%) were malignant, with 13 (16.5%) cases having a primary from the liver and 66 (83.5%) having metastasis from other primary sites, while 2 (2.4%) cases were reported as neoplastic masses without further categorization into primary or metastasis.

Based on histopathological findings, most of the patients with malignant liver masses were found to have Metastatic Adenocarcinoma (28; 35%), followed by Poorly Differentiated Carcinoma (13; 16.25%), Hepatocellular Carcinoma (10; 12.5%), Metastasis from Infiltrating Ductal Carcinoma of No Special Type (8; 10%), Poorly Differentiated Malignant Neoplasms (7; 8.75%), Metastatic Small Cell Carcinomas (7; 8.75%), Metastatic Squamous Cell Carcinomas (5; 6.25%), Poorly Differentiated Malignant Neoplasm Favoring Sarcoma (1; 1.25%), and 1 (1.25%) case of Neuroendocrine Tumor. The benign lesions included one case of a hydatid cyst and one of cavernous hemangioma.

Based on immunohistochemical findings, out of all the malignant liver lesions, the primary hepatocellular carcinoma cases were 9 (11.25%) [Fig. 2]. One case reported as hepatocellular carcinoma on histopathology was determined to be metastasis from a well-differentiated neuroendocrine tumor of the kidney on immunohistochemistry. The one case reported as poorly differentiated malignant neoplasm favoring sarcoma on histopathology was given a final diagnosis of Epithelioid Hemangioendothelioma on immunohistochemistry. The metastatic tumors were further classified using appropriate markers. Out of the 70 metastatic cases, the maximum number of cases had primaries from the lung (22; 31.42%) [Fig. 3], followed by pancreatico-biliary (19; 27.14%) and breast (13; 18.57%), while the remaining cases had primaries from colorectum (5; 7.14%), lymph nodes (3; 4.28%), and kidney (2; 2.85%). The other miscellaneous cases (6; 8.57%) included Metastatic Malignant Melanoma and primaries from the stomach, esophagus, larynx, cervix, and periampullary region [Fig. 4].

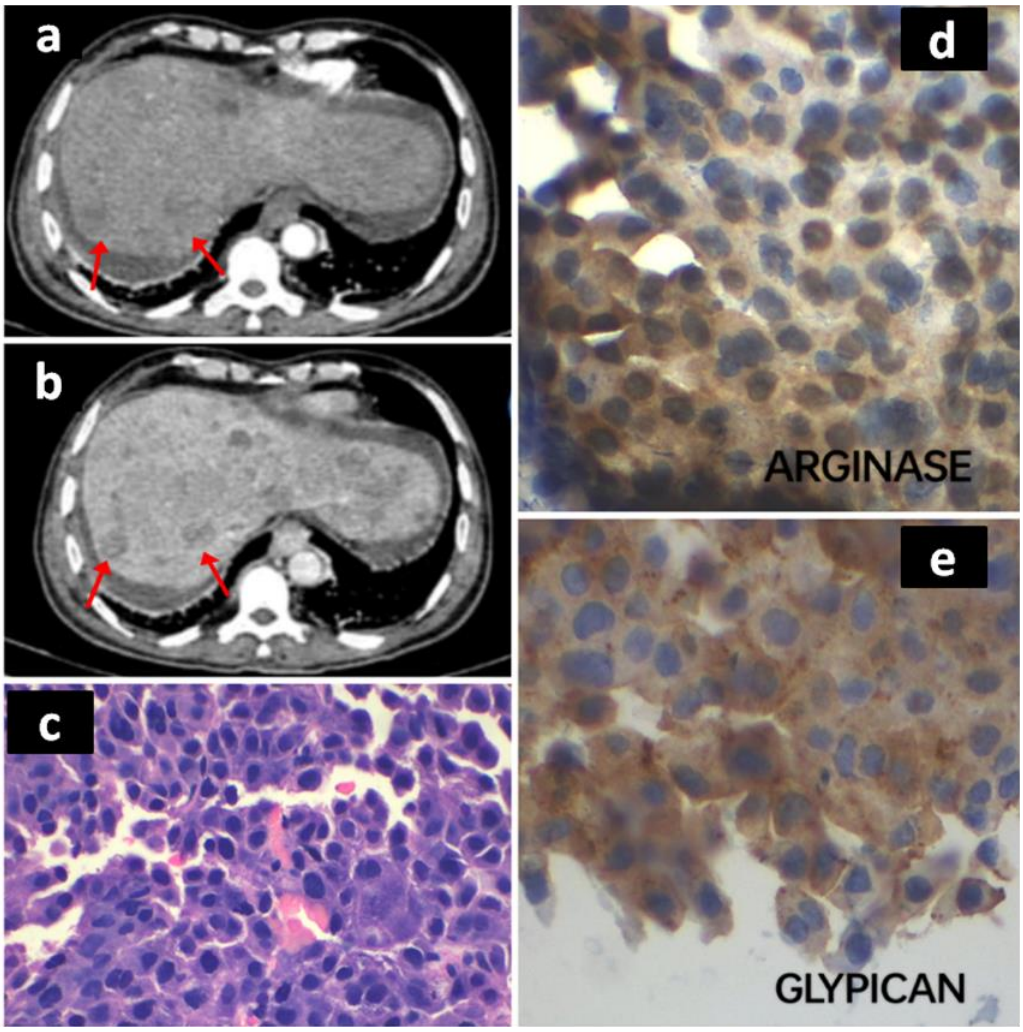

Figure 2: Hepatocellular Carcinoma- (a)Triple phase CT Angiography Abdomen Arterial phase showing multiple arterial phase enhancing lesions (red arrows) in both lobes of liver largest measuring 18x17mm in segment 7. (b) Venous phase – Hypodense lesions in liver (red arrows) showing early washout on portal venous phase, possibly Multifocal HCC. (c)High power view of liver biopsy showing atypical polygonal cells present in solid sheets and pseudoglandular pattern (H&E, 400x). Immunohistochemistry showing nuclear and cytoplasmic positivity for Arginase (d) and cytoplasmic positivity for Glypican-3 (e) confirming hepatocellular differentiation (400x).

In males, the maximum number of metastatic cases had primary from the lung, while in females, the most common primary was from the breast. In the lung (22; 31.42%), most of the cases were of the histologic type Small Cell Carcinoma (11; 50%), followed by Adenocarcinoma (5; 22.7%), Squamous Cell Carcinoma (5; 22.7%), and Mesothelioma (1; 4.5%). The metastatic tumors from the stomach and periampullary region were Well-Differentiated Neuroendocrine Tumor and Neuroendocrine Carcinoma. All three metastatic cases from lymph nodes were High-Grade B-cell Non-Hodgkin Lymphomas. The metastases from the kidney included one case of Clear Cell Renal Cell Carcinoma and one case of Well-Differentiated Neuroendocrine Tumor. The metastatic cases from the esophagus, stomach, larynx, and cervix were of histologic type Squamous Cell Carcinoma, while all the cases from pancreaticobiliary and colorectal origin were Adenocarcinomas. All 13 cases from breast primary were Infiltrating Ductal Carcinomas of No Special Type [Table 1].

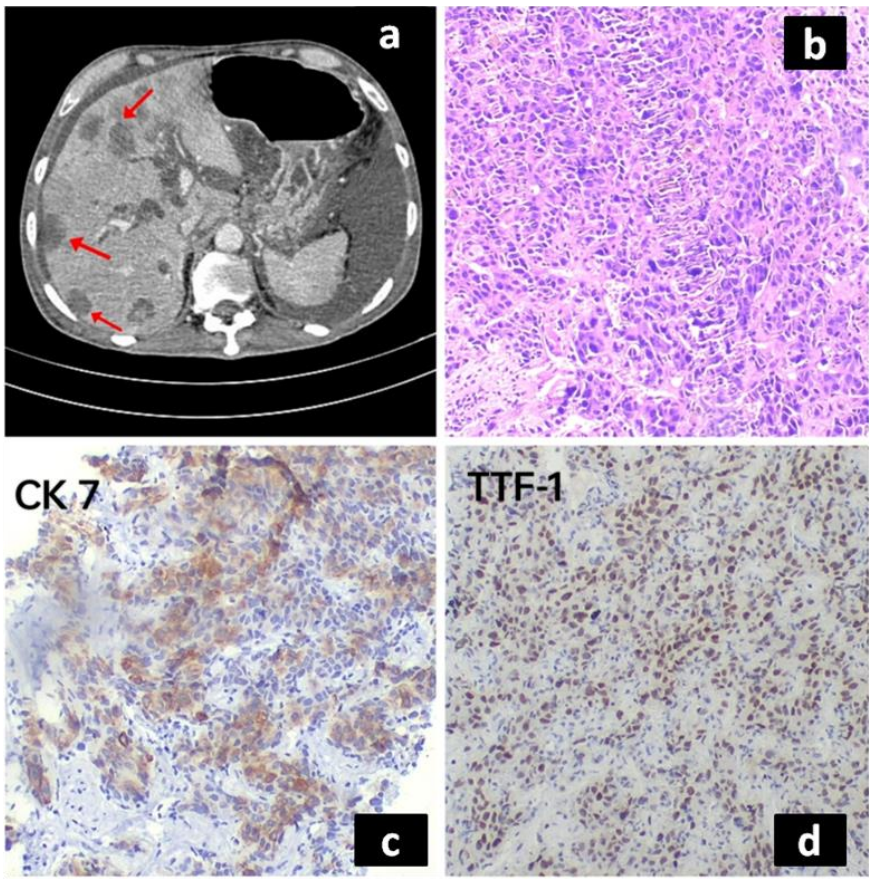

Figure 3: Metastatic Adenocarcinoma – Lung. (a) CECT Abdomen showing multiple hypodense lesions (red arrows) in both lobes of liver, largest measuring 31x30mm in segment 5. (b) Core needle biopsy of liver showing invasive sheets and acini composed of poorly differentiated atypical cells (H&E, 100X). Immunohistochemistry showing cytoplasmic and membrane positivity for Cytokeratin 7 (c) and nuclear positivity for Thyroid transcription factor-1 (d) confirming lung origin (100x).

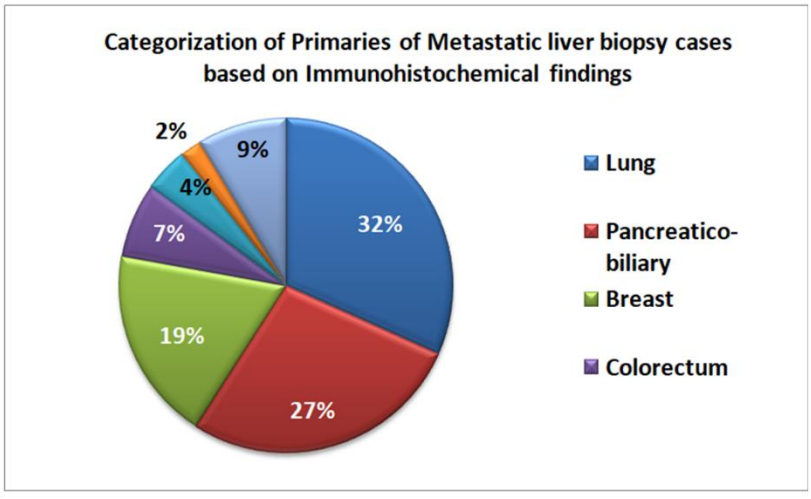

Figure 4: Pie chart depicting Primaries of Metastatic liver biopsy cases categorized on the basis of Immunohistochemical findings.

Table 1: Tabulation of Radiological, Histopathological and Immunohistochemical findings

Parameter	Radiological findings	Histopathological findings	Immunohistochemical findings
Benign	1	2	2
Primary tumor of liver	15	11	10
Metastatic tumors	66	79	70
Total Cases	82		

The sensitivity, specificity, negative predictive value, positive predictive value, and diagnostic accuracy of histology-proven immunohistochemistry in differentiating benign and malignant liver lesions were 50.00%, 100.00%, 98.77%, 100.00%, and 98.78%, respectively. The p-value was statistically significant ($p < 0.024$) [Table 2].

Table 2: Comparison of Radiological and Histopathology proven Immunohistochemical findings to differentiate Malignant and Benign lesions of liver.

		Histopathology proven Immunohistochemistry			
	Type	Malignancy	Benign	**Grand Total**	P Value
Radiology	Malignancy	80	1	81	
	Benign	0	1	1	0.024
	Total	80	2	82	

Discussion

Liver lesions are commonly encountered and frequently biopsied to categorize them as benign or malignant. Malignant lesions are further categorized as primary or metastatic based on histomorphological and immunohistochemical findings. Hepatic metastasis is much more common than primary liver lesions and is the second most common metastatic site after lymph nodes [6]. The present study, done to correlate the radiological, histopathological, and immunohistochemical findings of various liver masses, included a total of 82 cases.

The mean age observed in our study was 58.37 years, similar to studies done by Khadim et al. [6] and Khalifa et al. [2], who reported a mean age of 51 ± 3.7 and 62 ± 13 years, respectively, while Babar et al. [1] reported that the maximum number of cases (44%) were in the age group of 41–60 years, with a mean age of 51.25 years. The number of males in our study was predominant and included 47 (57.3%) cases, while females accounted for 35 (42.6%) cases. This finding was in concordance with studies done by Babar et al., Khalifa et al., and Khadim et al., who also reported a male preponderance [1,2,6].

The total number of malignant cases in our study was 80, of which metastatic cases accounted for the maximum number of cases—70 (87.5%)—while primary hepatic tumors accounted for 10 (12.5%) cases, consistent with studies by Babar et al. and Khalifa et al. [1,2]. Most of the metastatic liver lesions on radiology showed multiple lesions, similar to the radiological findings observed by Khalifa et al. and Khadim et al. in their studies [2,6].

Adenocarcinomas accounted for the maximum number of cases in the present study, which was in concordance with studies done by Babar et al. [1], Khalifa et al. [2], and Khadim et al. [6]. To narrow down the probable differential diagnosis, histological features are usually helpful for formulating a primary diagnosis so that appropriate markers can be applied accordingly. The most common site of the primary tumor observed in our study was the lung (22 cases, 31.42%), followed by the pancreatico-biliary system (19 cases, 27.14%), the breast (13 cases, 18.57%), and others. Khadim et al., in a study including 130 metastatic liver

cases, reported the most common primary site as the gastrointestinal tract, comprising 59 (45.3%) cases, followed by neuroendocrine tumors with 14 (10.7%) cases, gallbladder with 13 (10%) cases, and the lung with 8 cases (6.15%) [6]. Khalifa et al. included 210 metastatic liver biopsies and reported primary sites mostly from breast, colorectal, pancreas, and lung carcinomas [2].

Hepatocellular carcinoma mimics metastatic adenocarcinoma, cholangiocarcinoma, renal cell carcinoma, and adrenocortical tumors. A panel of immunohistochemical markers, including CK7, CK20, CD10, CEA, Hep Par1, and AFP, is useful for defining the primary site in such cases [6]. The second most common tumors metastasizing to the liver are neuroendocrine tumors [8]. Our study showed 13 cases of neuroendocrine tumors metastasizing to the liver. These can be identified by using specific immunohistochemical markers such as synaptophysin, chromogranin, and CD56. There is no single specific panel that can be used for all cases of metastatic hepatic tumors. The best selection of immunohistochemical markers will depend on the clinical history, radiological findings, histomorphological features, and other relevant investigations.

The sensitivity, specificity, negative predictive value, positive predictive value, and diagnostic accuracy of immunohistochemistry observed in our study were 50.00%, 100.00%, 98.77%, 100.00%, and 98.78%, respectively. Babar et al. reported sensitivity, specificity, positive predictive value, and negative predictive values of 88.23%, 93.75%, 85.33%, 90.90%, and 88.23%, respectively [1]. Khalifa et al. observed a sensitivity of 90% in their study [2]. Ali et al., in a study comparing Doppler sonography findings with histopathology and cytopathology, reported a sensitivity of 94.5%, specificity of 91%, diagnostic accuracy of 93%, positive predictive value of 92%, and negative predictive value of 93.9% [9].

Limitations: There are some possible limitations in this study. Since the present study is a retrospective analysis, limited data availability was a potential limitation. Interobserver variability in selecting immunohistochemical panels was another limitation, as the blocks were outsourced for immunohistochemistry. Our study was performed in a single center, which may limit the generalizability of the results. Additionally, the number of passes done was not routinely documented, so we could not correlate the number of passes with the ability to make a diagnosis.

Clinical Implications and Future Perspectives: The authors suggest that the role of biopsy followed by immunohistochemistry might be relevant from both clinical and therapeutic perspectives. Immunohistochemical markers are now increasingly being used for molecular-targeted therapies and for predicting therapeutic response. Immune biomarkers such as anti-PD-1, anti-PDL-1, and anti-CTLA-4 are useful for deciding adjuvant therapy [10]. Hepatocellular carcinomas expressing CK19 are known to show aggressive behavior, high proliferative index, poor differentiation, and a high recurrence rate [4]. Newer molecular analyses may help determine the most appropriate chemotherapeutic agents. Genetic alterations are key determinants of tumor sensitivity to targeted therapies. Targeting particular subsets of tumors remains a promising approach, as shown by the recent success of the REACH-2 trial, which assessed the efficacy of an antiangiogenic drug—ramucirumab—in patients with raised alpha-fetoprotein levels [11]. With the advent of next-generation sequencing, gene expression arrays, and computational pathology, these technologies are likely to drive the next major revolution in personalized medicine [12].

Conclusion

The present study concludes that despite advancements in imaging techniques, histopathological assessment followed by immunohistochemistry remains the gold standard for accurately diagnosing various liver lesions with good specificity, positive predictive value, negative predictive value, and diagnostic accuracy. Integration and correlation of both radiological and

pathological findings will provide better diagnostic accuracy, leading to improved patient care, prognosis, and overall survival.

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Conflicts of Interest: The authors have no conflicts of interest to declare.

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Competing Interests: None declared.

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