Mini-Review

Hepatobiliary-specific magnetic resonance contrast agents: role in biliary trauma

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Abstract: Non-iatrogenic traumatic bile duct injuries (NI-TBIs) are a rare complication after abdominal trauma, with an estimated prevalence of 2.8–7.4% in patients underwent blunt liver injuries. They may be overlooked in patients with extensive multi-organ trauma, particularly hepatic, splenic and duodenal injuries, which have a prevalence of 91%, 54% and 54%, respectively. Whole body contrast-enhanced computed tomography (CE-CT) represents the examination of choice in polytraumatized hemodynamically stable patients, as it allows a comprehensive evaluation of vascular, parenchymal, bone and soft tissues injuries, but the diagnosis of any biliary leaks is limited to the evaluation of nonspecific imaging findings and on findings evolution in the follow-up, such as the progressive growth of fluid collections. Furthermore, biliary complications, such as the occurrence of biloma or biliary peritonitis, may become manifest several days after the initial trauma, often with unspecific progressive signs and symptoms. Although CT and ultrasonography can suggest bile leaks based on several nonspecific imaging findings (e.g., fluid collections), magnetic resonance imaging (MRI) using hepatobiliary contrast agents helps to identify the site and entity of post-traumatic biliary disruption. Indeed, MRI allows to obtain cholangiographic sequences that may show post-traumatic active bile leakage and cysto-biliary communications by direct visualisation of contrast material extravasation into fluid collections, increasing the preoperative accuracy of NI-TBIs. Few data are available about MRI use in the follow-up of trauma with NI-TBI management. So, in the present mini review, its role is reviewed and our preliminary experience in this field is reported.

Keywords: Liver trauma; biliary trauma; magnetic resonance-cholangiography (MR-cholangiography); magnetic resonance imaging (MRI); biliary tree

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Background

Non-iatrogenic traumatic bile duct injuries (NI-TBIs) are a rare but complex result of abdominal trauma and an important source of morbidity in the short and long term. They account for approximately 1–5% of the total number of biliary injuries, with a prevalence of 2.8–7.4% after blunt hepatic injuries or penetrating injuries caused by simple direct force, as knife wound, or by a complex, indirect injury, as gunshot wound (1-3). Moreover, NI-TIBI may be overlooked in patients with extensive multi-organ trauma, as in case of hepatic, splenic and duodenal injuries, which have a reported prevalence of 91%, 54% and 54%, respectively. They may present in a spectrum of conditions ranging from more severe cases, as full biliary transections or partial lacerations, to simple contusions and wall hematomas (1,2). Isolated NI-TBIs are extremely rare, occurring in only 2–3% of cases (4). Similarly, gallbladder injury is an uncommon occurrence following trauma, occurring in 2% of cases, because of the protective effect of the liver (4). A majority (89%) of gallbladder injuries resulted from penetrating trauma (4,5). Nevertheless, as the adoption of non-operative management (NOM) in the initial treatment of abdominal traumas has increased, this patient population has grown significantly (1,5-11). The identification of NI-TBI may represent a diagnostic challenge due to their lack of specific signs and symptoms. Furthermore, a delay in the recognition of biliary leaks leads to poor outcomes and high mortality rates also related to associated injuries (e.g., pancreatic ductal injuries) (2,4,7,12).

Imaging plays a crucial role in formulating a correct and timely diagnosis to improve patient management (*Table 1*) (2). Whole body contrast-enhanced computed tomography (CE-CT) represents the examination of choice in polytraumatized hemodynamically stable patients, as it allows a comprehensive evaluation of vascular, parenchymal, bone and soft tissues injuries (3,13-17) but the diagnosis of any biliary leaks is limited to the evaluation of nonspecific imaging findings and on findings evolution in the follow-up, such as the progressive growth of fluid collections.

In the nonoperative management approach, CE-CT is preferred when the patient has multiple injuries, not allowing for an exclusive imaging evaluation of each of them (7,9).

Ultrasound (US) or contrast-enhanced US (CEUS) can be used as an alternative to CE-CT for the re-evaluation of fluid collection (2,4,9,10). On the other hand, hepatobiliary scintigraphy and magnetic resonance imaging (MRI) can help to detect active or contained bile leaks (2). However, hepatobiliary scintigraphy has some major limitation related with the low anatomic definition and low spatial resolution, as well as long scan times and poor resource availability, and so it is not appropriate for detection of biliary leak in patients with suspected post-traumatic gallbladder and biliary injuries. MRI has an emerging role in the study of liver trauma and biliary complications eventually associated. Indeed, MRI allows a detailed study of the biliary anatomy, thanks to a high signal-to-noise ratio in the biliary tree with T2-weighted (w) sequences and functional informations that can be obtained using hepatobiliary-specific contrast agents (2,3,9).

Pathophysiology and classification

NI-TBI in the form of blunt and sharp trauma should be considered when a patient presents following a penetrating lesion or an appreciable blunt force injury to the right thoracoabdominal region (1,2,4,7,12,18,19). In the former case, trajectories of objects under the influence of gravity are evaluated in cuts; conversely, in gunshot wounds, because the trajectory is variable, the path of injury may be less obvious (18,19). In the latter case, the mechanisms of injury include assaults, falls and deceleration injuries of motor vehicles (1,2,4,7,12,18,19). Timely identification of the injury is imperative to minimise the morbidity associated with untreated trauma bile injuries, such as portal hypertension, cholangitis or cirrhosis (1,2,4,7,12,19). The development of clinical signs and symptoms such as right upper quadrant pain, fever, jaundice or melena suggests liver-related complications (1,2,4,7,10,12,19). Laboratory findings may include leucocytosis and abnormal liver function tests, but no specific laboratory tests exist to diagnose traumatic bile duct injuries (1,2,4,7,12,19).

NI-TBIs include bile leakage (i.e., biloma and biliary fistula), haemobilia and bile duct stricture. They can be distinguished in intrahepatic and extrahepatic. Intrahepatic bile duct injuries are always associated with liver parenchymal lacerations. Conversely, isolated extrahepatic biliary injury extremely rarely occurs (7,19).

However, NI-TBIs are associated with liver, pancreas or duodenum injury in the vast majority of cases. In case of intrahepatic bile duct injuries, small subsegmental bile ducts are most commonly affected; however, the major intrahepatic ducts may also be injured. Such lesions can be further subcategorised according to the region of involvement of the biliary tract, in central and peripheral bile duct injuries. Intrahepatic biliary injuries are considered

Table 1 Imaging techniques in biliary trauma

Imaging method	Role	Advantages	Disadvantages
CE-CT	First line imaging methods in high energy traumas	Fast whole-body imaging evaluation	Relatively low resolution for biliary structures
		Some findings, as liver lacerations, fluid or spontaneously hyperdense collections may suggest the presence of biliary trauma	Cannot directly demonstrate bile duct injuries
		Prompt detection of active bleeding	
MRI	High resolution for biliary structures	Extremely high resolution for biliary structures	Examination time
	Useful as second line imaging modality in case of suspected biliary injuries	Availability of specific contrast media with biliary excretion	Limited availability
		Direct identification and location of biliary extravasation in the majority of cases	Claustrophobia, not compatible implants
US	Follow-up of liver and biliary trauma (e.g., evaluation of bilomas and fluid collections), eventually with intravenous contrast medium.	Bed side examination	Limited panoramicity
		Availability	Cutaneous bandages or injuries may limit the examination
ERCP	Diagnostic confirmation and therapy	Therapeutic role (e.g., sphincterotomy, biliary stent placement)	Invasiveness
			Availability
Hepatobiliary scintigraphy	Not recommended for detection of biliary leak	Demonstrates biliary excretion	Poor anatomic definition
			Poor spatial resolution
			Long scan times
			Limited availability

CE-CT, contrast-enhanced computed tomography; MRI, magnetic resonance imaging; US, ultrasound; ERCP, endoscopic retrograde cholangiopancreatography.

central when they are localised within 5 cm from the hepatic duct bifurcation, and peripheral when they involve biliary ducts located more than 5 cm away from the hepatic duct confluence (1,2,12). Extrahepatic bile duct injuries may involve the biliary bifurcation, the hepatic duct, the cystic duct, or the common hepatic duct. The gallbladder is another potentially involved site in cases of extrahepatic biliary tree injury. Its perforation may more often occur after penetrating injury. Extrahepatic bile duct injuries are generally found in the points of anatomical fixity, such as the intrahepatic tract of the common bile duct, and are generally related to traumas from abrupt deceleration (1,2,4). These types of injuries are less frequent than intrahepatic injuries and may be associated with lesions of the hepatic artery or of the portal venous system, that can lead to biliary ischemia and stricture formation.

Bile leaks may be simple or complex (e.g., when superinfection occurs) and are usually classified as major or minor. Major leaks are those with drainage of more than 400 mL/d or persistent drainage of more than 50 mL/d for more than 14 days, whereas minor ones are those with bile drainage of less than 400 mL/d or greater than 50 mL/d but for not longer than 14 days (1,2,4,20). Furthermore, biliary injuries in patients with liver trauma may manifest as simple bile leaks into the lacerated liver, into the peritoneal or pleural cavity, or may also result in biliary-vascular fistulae (1,2,7).

Considering the American Association for the

Surgery for Trauma (AAST) organ injury scale and the haemodynamic status, both intrahepatic and extrahepatic bile duct injuries are currently graded as minor, moderate or severe (4).

Management implications

NOM of traumatic liver injury is currently regarded as the standard of care for hemodynamically stable patients, whereas the use of damage-control techniques is recommended for those who are hemodynamically unstable (4,7,9,10,15,20,21). This therapeutic approach has led to increased survival, making bile leak a more common complication. Most traumatic bile leaks are minor, usually recovering well after conservative treatment. Conversely, major bile leaks require prompt diagnosis and effective treatment to prevent the development of further complications such as biloma, infection or intra-abdominal sepsis (5,7,19).

Given their frequent association with multiorgan injuries and infection and their often-delayed diagnosis due to the insidious clinical presentation, NI-TB leaks are a complex problem requiring a multidisciplinary team approach involving radiologists, endoscopists and surgeons. Surgery has been the preferred treatment for post-traumatic bile leaks. However, it can become difficult in presence of adhesions, inflammation and liver parenchyma lacerations, being associated with high rates of morbidity and complications. Thus, as for iatrogenic bile leaks, in the absence of complete circumferential transection of the main bile duct or common hepatic duct, endoscopic management with biliary plastic stent insertion for 4 to 8 weeks without routine sphincterotomy is currently recommended as first-line therapy. Furthermore, endoscopic placement of a biliary fully-covered self-expandable metal stent may be valuable in cases of refractory bile leak (4,22). Therapeutic endoscopic retrograde cholangiopancreatography (ERCP) is a non-operative approach that allows to decrease or eliminate the pressure gradient between the bile duct and duodenum, addressing the preferential bile flow from the duct into the duodenum instead of bile exiting the leakage site. The absence of ongoing bile flow through the leak site results in defect healing in the vast majority of cases (22,23). Conversely, in cases of complete circumferential interruption of the common bile duct or common hepatic duct, a large-calibre, high-quality surgical hepaticoenterostomy is recommended (4,22).

In case of unreconstructable biliary injury, hepatic and pancreatic resections may be required. In case of gallbladder injury, cholecystectomy is the gold standard treatment (4).

Diagnosis and imaging role

The diagnosis of NI-TBIs is not simple as clinical signs and symptoms of bile leaks can be unspecific but, a delay in their recognition is led to higher morbidity and mortality. Therefore, imaging is very important to reach an early diagnosis and to guide the treatment algorithm (*Table 1*) (2). The most appropriate imaging method to be adopted in this setting depends on the patient's condition, the type of injuries to look for, the presence of concomitant injuries and the biological invasiveness of each imaging method (9,10,15,21). The diagnosis of NI-TBIs is usually based on clinical suspicion, and CE-CT is routinely used as a referred imaging modality (2,4,7,9,12). The major CE-CT features of injury to the intrahepatic bile ducts are a consequence of the influx of bile into the hematoma, which may increase the pressure within the hematoma, leading to necrosis of the surrounding liver tissue and formation of a biloma (2). The progressive growth of well-circumscribed, low-attenuation intraparenchymal or perihepatic fluid collections on CE-CT strongly suggests the diagnosis of bile leaks. However, although the presence of free fluid is sensitive, it is nonspecific for bile leakage, so CT cannot directly demonstrate bile duct injuries. Imaging-guided percutaneous aspiration is needed to confirm the diagnosis of biloma in symptomatic patients (2). US with or without contrast media is mostly limited to the follow-up of complications such as biloma or targeted drainage (2,21). ERCP is a very accurate tool for bile duct evaluation, providing excellent delineation of the anatomy of the injured biliary ductal system, defining the type of injury and clearly documenting the extravasation of injected contrast material in cases of bile leaks. However, given its invasiveness, ERCP is rarely performed with a solely diagnostic purpose (4,24). Hepatobiliary scintigraphy demonstrates physiologic biliary excretion, however, it is limited by low anatomic definition and low spatial resolution, as well as by long scan times and poor resource availability, so it is not indicated for detection of biliary leak in patients with suspected gallbladder and biliary injuries in the trauma setting (2,4). CE-MRI with hepatobiliary contrast agents is gaining an emerging role in the study of liver trauma and related biliary complications. MRI allows to obtain both a good detail of the biliary anatomy, thanks to a higher signal-to-noise ratio in the bile duct with conventional T2w sequences, and functional information after the injection of hepatobiliary specific contrast agents. CE-MRI using hepatobiliary contrast agents increases the preoperative accuracy of identifying and locating extravasations of bile in liver trauma with higher sensitivity compared to CE-CT (2,9,10,25). Hepatobiliary contrast agents are excreted into the biliary tree, shorten the T1 relaxation time of the bile so allowing to acquire high-resolution T1w contrast-enhanced cholangiographic imaging sequences giving, in addition to conventional T2w sequences, valuable information about biliary anatomy, allowing accurate detection of biliary injury complications, such as biliary fistulas and bilomas, identified as progressive fill-in during the hepatobiliary delayed phase imaging (2,9,10,25). Gadobenate dimeglumine (Gd-BOPTA, MultiHance, Bracco, Milan, Italy) and gadoxetic acid (Gd-EOB-DTPA, Primovist in Europe; Eovist in the USA; Bayer Healthcare, Leverkusen, Germany) are the hepatobiliary-specific agents approved by the Food and Drug Administration for clinical use. Both of them are considered 'combination agents' due to their dual capability for imaging in the dynamic and delayed hepatocyte-specific phase (26-28).

MR personal experience

Few data are now available about MRI use in the follow-up of trauma with NI-TBI management (4,10,25,29,30). We report our preliminary experience in this field. The imaging protocol is not standardised but adapted according to the type of patient. It is based on both the type of lesion to be characterised and the complications eventually present at the time of the examination (9,10,25). This approach allows for reducing the time of examination, also making it possible to perform MRI examinations in less cooperative patients. In our Institution, MRI examinations are performed from the 2nd–3rd day after trauma to monitor the evolution of injuries detected at CT scan, or to clarify doubtful CT findings. Exclusion criteria include hemodynamically unstable patients, those with MRI-incompatible implants or devices, and patients with claustrophobia (9,10,25). In our Department, MR examinations are acquired with a high-field magnet (SIGNA, 1.5 T magnet, General Electric Company, Boston, MA, USA) equipped with a phased-array superficial coil. In cooperative patients, breath-hold imaging is adopted to avoid artefacts, whereas, in uncooperative patients, respiratory gating is used (9,10,25). Standard imaging sequences are multiplanar T2w single-shot fast-spin echo (SSFSE) and axial T2w SSFSE sequences with fat suppression (FS) for morphological imaging and to delineate parenchymal injuries, axial T1w gradient echo (GRE) in- and out-of-phase to recognise fatty infiltration and to evaluate stage of haemoglobin degradation, axial diffusion-weighted imaging to observe the restriction characteristics of parenchymal injuries, radial and three-dimensional (3D) magnetic resonance cholangiopancreatography (MRCP) images to obtain good anatomic details of the biliary and pancreatic ductal system in patients with suspected biliary and pancreatic injuries, axial GRE T1w 3D FS pre-contrast for haemoglobin degradation, and the same dynamic contrast-enhanced sequence after intravenous administration of a gadolinium contrast agent for the detection of contained vascular injuries, active bleeding, and to evaluate the parenchymal intensity (9,10,25). In the suspicion of biliary leaks, the choice of contrast medium falls on the use of hepatospecific ones, which, after the dynamic phase to exclude vascular lesions or active bleeding, also adds a late phase of biliary excretion 90–120 minutes after intravenous administration of Gd-BOPTA or 15–20 minutes after intravenous administration of Gd-EOB-DTPA, obtaining the hepatobiliary delayed phase imaging useful for the diagnostic definition of biliary leaks.

Discussion

Hepatocyte-specific contrast agents, once intravenously injected, are preferentially taken up by hepatocytes and their elimination is a combination of biliary and renal clearance. Particularly, 50% of Gd-BOPTA is excreted in the biliary system approximately starting from 20 minutes after injection, with a shorter total acquisition time compared to Gd-EOB-DTPA of which just 5% is excreted in the biliary system in longer times. So in the study of traumatised patients, it is preferable to adopt Gd-BOPTA to short examination time. However, bilirubin value should be evaluated before administration as bilirubin competes with the hepatobiliary contrast agent, so patient with hyperbilirubinemia may have reduced uptake and excretion of the hepatobiliary contrast agent, particularly if direct bilirubin value is greater than 2.18 mg/dL (26).

With the GRE T1w 3D FS sequence, the contrast agent excretion into the biliary tree causes hyperintensity of bile that is visualised in the multiplanar plane. The latter is a true cholangiographic sequence allowing for the detection of post-traumatic active bile leakage and eventually present cysto-biliary communication, by direct visualisation of contrast material extravasation into fluid collections, also

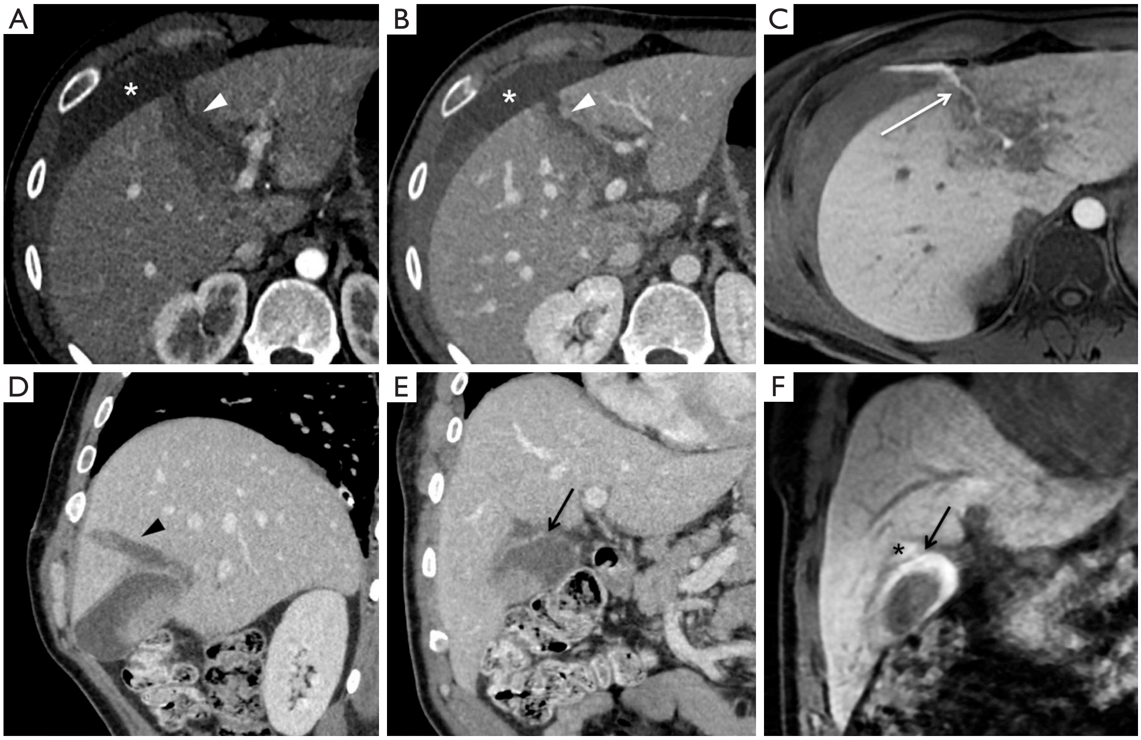

Figure 1 Examples of extrahepatic biliary leak after abdominal trauma. Upper row: extrahepatic biliary leak in a 34-year-old woman referred to an ED after abdominal blunt trauma from an accidental fall from a bicycle. Arterial (A) and portal (B) phases at admission CT scan showed IV segment liver laceration (white arrowheads) with hemoperitoneum (white asterisk) but no active bleeding. Control liver MRI performed 14 days after trauma showed perihepatic fluid collection associated with a biliary leak (white arrow) at hepatobiliary phase scan acquired after 30 minutes from gadoxetate disodium contrast agent administration (C). Bottom row: extrahepatic biliary leak in a 54-year-old man referred to an ED after perforating abdominal trauma from an accidental fall from a tree (penetrating trauma from a 15-cm-long wooden tree branch). Sagittal (D) and coronal (E) portal phase CT scan reconstruction at admission showed penetrating liver injury (black arrowhead) resulting in gallbladder wall perforation (black arrow). Subsequent MRI hepatobiliary phase scan acquired after 30 minutes from gadoxetate disodium contrast agent administration (F) confirmed gallbladder wall laceration (black arrow) and associated biliary leak (black asterisk). ED, emergency department; CT, computed tomography; MRI, magnetic resonance imaging.

showing the anatomical site and the type of bile duct injury (*Figures 1,2*). Both agents are currently administered by automatic injection followed by a saline solution flush. Gd-BOPTA is administered at the dosage of 0.05 mmol/kg (0.1 mL/kg of the 0.5 M solution), with a flow injection rate of 2–2.5 mL/s. Gd-EOB-DTPA is injected at the recommended dose of 0.025 mmol/kg (0.1 mL/kg of the 0.25 M solution). The hepatobiliary phase imaging delay time is shorter for Gd-EOB-DTPA in comparison with Gd-BOPTA, as Gd-EOB-DTPA has a biliary excretion of 50% whereas Gd-BOPTA of 5%. This approach shortened the total acquisition time for the study (10,26,27,28). Therefore, combined with a similar safety profile, Gd-EOB-DTPA is the preferred contrast agent for the detection of biliary leaks (10,26,27,28). However, Gd-BOPTA yields greater enhancement of liver vessels than Gd-EOB-DTPA does and better performance in dynamic phase imaging (10,26-28). However, liver function influences the image quality after the administration of hepatobiliary specific contrast agent and adequate contrast material filling in the bile duct can be obtained in normal or not substantially reduced liver function (10,26-28). Conventional T2w MRI should be acquired before the excretion of hepatobiliary contrast material into the biliary lumen, because it causes a shortening of the T2 relaxation time of bile and so interferes with the optimal visualisation of biliary fluid in this sequence (10,25-28). We strongly recommend performing a pre-contrast GRE T1W 3D FS

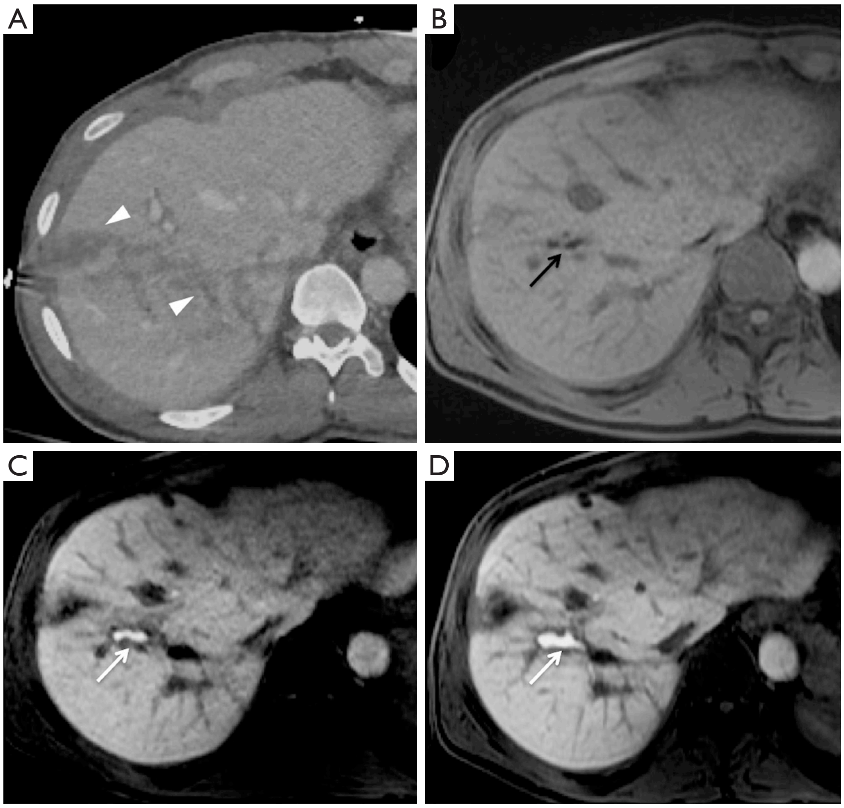

Figure 2 Example of intra-hepatic biliary leak after abdominal trauma. Biliary leak within liver laceration in a 43-year-old man referred to an ED after abdominal trauma due to a motor-vehicle accident. Portal phase at admission CT scan (A) show large VII–VIII segment liver laceration (white arrowheads); T1-weighted fat-saturated axial MRI scan acquired before contrast media administration (B) showed the absence of spontaneous T1 hyperintensities due to blood products in the selected MRI slice (black arrow); subsequent T1-weighted fat-saturated axial MRI scan at the same level acquired at 10 (C) and 35 (D) minutes after gadoxetate disodium administration showed a biliary leak within the liver laceration, with a collection slightly increasing in diameter over time (white arrows). ED, emergency department; CT, computed tomography; MRI, magnetic resonance imaging.

phase to correctly differentiate hyperintense coagulated blood in the subacute phase from a biliary leak in the hepatospecific phase, which appears hyperintense in the same way. We also strongly advise, when the case requires it, and the clinical suspicion is high, to add a very late acquisition sequence to exclude the presence of very small leaks (*Figures 1,2*). Main limitations are related to the acquisition times, that should be optimized specifically focusing the study on the already known injuries to be evaluated, to uncooperative patients, those with MRI-incompatible implants or devices, and patients with claustrophobia.

Conclusions

MRI with hepatobiliary specific contrast agents has very promising characteristics in the study of patients with biliary trauma, not including just the absence of a radiation dose, so it should be considered as a useful adjunctive tool in the re-evaluation of traumatized patients. We recommend performing CE-MRI with intravenous hepatobiliary contrast agents in the follow-up of hemodynamically stable patients with blunt liver trauma and suspected NI-TBI. CE-MRI with hepatobiliary contrast agents is a recently developed imaging approach that can increase the preoperative accuracy when identifying and locating sites of biliary extravasation in liver trauma.

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Footnote

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