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MODERN ADVANCES IN THE DIAGNOSIS OF ACUTE CALCULOUS CHOLECYSTITIS (A literature review)

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ABSTRACT

Diagnostic methods for acute calculous cholecystitis continue to evolve. Among the most common abdominal pathologies, acute calculous cholecystitis requires astute clinical judgment, highly accurate and correct diagnosis, adequate treatment, and timely surgical intervention. A wide range of diagnostic and grading programs have been developed, most remarkably the Tokyo Guidelines, but some recent clinical validation studies have questioned their applicability in practice. The timing of surgical intervention is another area that requires further study and improvements in the diagnosis of this disease.

Key words: acute cholecystitis, ultrasound, computed tomography, magnetic resonance imaging, hepatobiliary scanning, laparoscopic cholecystectomy.

INTRODUCTION

Gallstone disease (GSD) remains one of the most common diseases among the surgical pathology of the abdominal organs. In developed countries, 10–15 % of the adult population is affected by gallstones, with wide variation in severity (Ansaloni et al, 2016). However, the prevalence of GSD varies significantly between ethnicities and may exceed 30% of the population in some areas of the globe (Bitemirova, 2018). Moreover, according to Scandinavian scientists, the prevalence of gallstone disease increases with age. Ultrasound of the biliary system among Mexican Americans diagnosed cholelithiasis at the age of over 45 years old in 40.2% of women and 19.2% of men (Bitemirova, 2018). So, the prevalence is higher in women, in association with multiple pregnancies, obesity, rapid weight loss, and older patients. In many people, the course of cholelithiasis may run asymptomatic and never be diagnosed throughout their life. In 6-29% of cases, gallstones are found during postmortem examinations (Gadzhiev et al, 2013).

From 20 to 40% of patients with gallstones will develop gallstone-related complications, with an incidence of 1–3% annually. Acute calculous cholecystitis (ACC) is the first clinical presentation in 10–15% of the cases (Kimura et al, 2013). ACC is one of the most frequent and severe complications of GSD. It occurs in roughly 20% of patients with gallstones (Horn et al, 2014). One of the severest forms of ACC is gangrenous cholecystitis which has an incidence ranging from 2% to 29.6%, according to various surgical series (Hunt & Chu, 2000), and generally occurs in older patients. Gangrenous and necrotizing acute cholecystitis are severe advanced forms of the disease and are associated with higher morbidity and mortality than occur in uncomplicated acute cholecystitis. Moreover, the clinical and laboratory characteristics of patients with these advanced forms are often nonspecific and indistinguishable from those of patients with acute cholecystitis without gangrene. An increased incidence is seen in men and patients with coexisting cardiovascular disease and leukocytosis >17,000 WBC/mL (Wu et al, 2010). The clinical and sonographic Murphy sign was found to be positive in only 33% of these patients, most likely due to denervation of the gallbladder wall (Wu et al, 2010). This frequently causes diagnostic obscurity and further complications.

During the last decade, many authors suggested their principles of management for ACC. Despite the relevant frequency of this pathology, significant controversies remain regarding the diagnosis and management of ACC. The Tokyo guidelines 2007, 2013, and 2018 (TG) attempted to establish objective parameters for the diagnosis of ACC (Hirota et al, 2007; Yokoe et al, 2018). Furthermore, a group of scientists proposing WSES guidelines in 2016, improved diagnostic arrangements and recommended certain treatment tactics for ACC that were upgraded and enriched in 2020 by the same committee (Ansaloni et al, 2016; Pisano et al, 2020).

However, controversies continue in the diagnostic value of single ultrasound (US) signs, as well as of laboratory tests. Regarding the management of ACC, the main debates arose around the timing for surgical intervention. The method and indications for diagnosis (especially for invasive diagnostic modalities) of potential biliary tract stones associated with ACC, type of surgery, and risk stratification and definition for patients with ACC are the other major disagreements in modern ACC management. All controversies require a range of improvements in the diagnosis of ACC to be agreed upon and accepted unanimously.

Diagnosis of acute calculous cholecystitis

Diagnosis is the starting point of the management of ACC, and prompt and timely diagnosis should lead to early treatment and lower mortality and morbidity.

The Tokyo guidelines 2007 (TG07) proposed diagnostic criteria for acute cholecystitis. It was based on three main categories of ACC symptoms: local signs of inflammation like a) Murphy's sign and right upper quadrant (RUQ) mass/pain/tenderness; b) systemic signs of inflammation: fever, elevated C-reactive protein (CRP), an elevated WBC count; c) imaging findings characteristic of acute cholecystitis. According to the authors of the guideline, one item in the "a" and one item in the "b" are positive. Any findings characteristic for acute cholecystitis in "c" confirm the diagnosis of ACC when acute cholecystitis is suspected clinically (Hirota et al, 2007). The authors claimed that at the end of the discussion of the Tokyo International Consensus Meeting, the unanimous agreement had been achieved on the diagnostic criteria. However, almost 20 % of the foreign panelists of the meeting expressed the necessity of some modifications based on further imaging modalities which were ignored.

Hepatobiliary Scan

Cholescintigraphy or hepatobiliary scintigraphy is a special radiographic method of diagnosis for the hepatobiliary tract and gallbladder pathologies. Cholescintigraphy – is a form of medical imaging, is also popular by other names depending on the type of radiotracer is utilized, such as HIDA scan, PIPIDA scan, DISIDA scan, or BrIDA scan. A specially targeted chemical radio-element (radioactive tracer) is injected through the vein of the patient and then allowed to circulate to the whole body including the liver, where the element is excreted into the bile ducts and stored by the gallbladder until released into the duodenum.

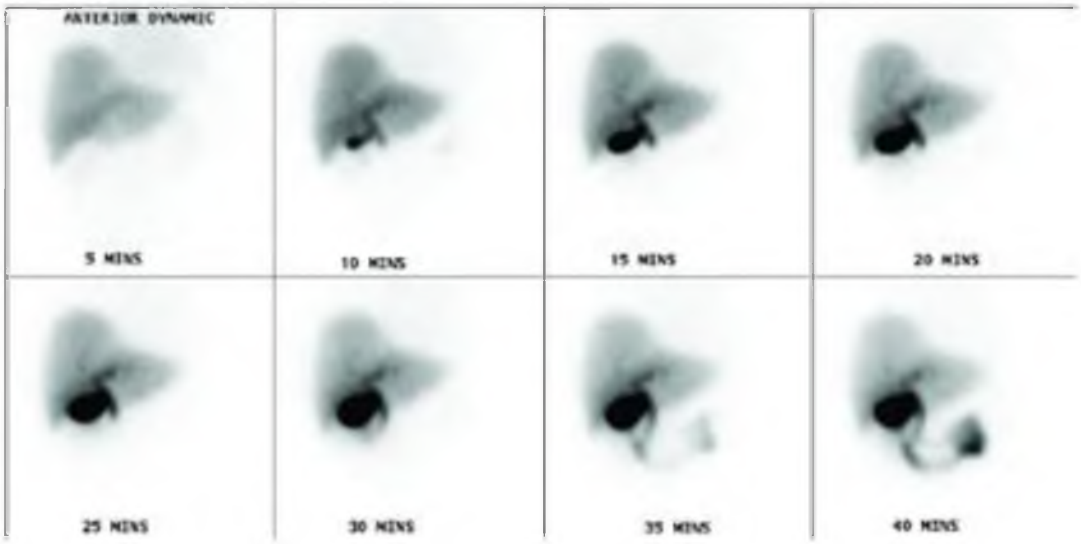

Figure 1. ***Normal hepatobiliary scintigram*** *(adopted from www.sgsnuclearmedicine.com)*

In 1994, Shea et al reported a systematic review of imaging studies published between 1978 and 1990. In this review, they concluded that cholescintigraphy had the best sensitivity (97%; 95% confidence interval [CI]: 96%, 98%) and specificity

(90%; 95% CI: 86%, 95%) in the detection of acute cholecystitis, whereas US had a sensitivity of 88% (95% CI: 74%, 100%) and a specificity of 80% (95% CI: 62%, 98%). It is uncertain whether these accuracy estimates still hold almost 30 years later, given that more accurate studies have been published since 1990. In the practice, Wertz et al. (2018) used HIDA scan effectively in case of ambiguity of CT and US for ACC. There has also been substantial technological improvement in imaging techniques during the last 3 decades (e.g., improved resolution and the use of Doppler imaging in US), and newer modalities have been introduced.

Ultrasound Scanning

The authors of 2016 WSES guidelines on acute calculous, which was updated in 2020, suggested combining the results of detailed history, complete clinical examinations, and laboratory tests to enhance the accuracy of diagnosis of ACC (Ansaloni et al, 2016). Abdominal US was highly recommended by the authors of TG13, TG18, and WSES 2020 guidelines as the preferred initial imaging technique for patients with the clinical suspect to have ACC due to its ubiquity, lower economic cost, less invasiveness, and high accuracy for gallbladder stones and real-time character (Hirota et al, 2007; Yokoe et al, 2013; Pisano et al, 2020; Mathur et al, 2017). The sensitivity of US for ACC in individual studies in which US was evaluated ranged from 50% to 100%, while specificity was between 33% and 100%. The summary estimate of sensitivity was 81% (95% CI: 75%, 87%) at a specificity of 83% (95% CI: 74%, 89%) (Kiewiet et al, 2012).

The diagnostic performance of US in the detection of inflammation of the gallbladder is not as good as its performance in the diagnosis of cholelithiasis (Kuhlenschmidt et al, 2021). For instance, in another interesting research conducted by Hwang et al. (2014) on 107 patients, 54 % (95 % CI: not reported) and 81 % (95 % CI: not reported) were reported for sensitivity and specificity respectively by using the combination of major clinical symptoms like sonographic Murphy sign, thickening of gallbladder wall more than 3 mm, presence of pericholecystic fluid and minor diagnostic criteria such as hepatic biliary dilation and gallbladder hydrops. Another similar study was accomplished by Borzellino et al. (2015) in which a multivariate analysis of 186 patients was performed for clinical criteria. According to the results of that analysis, GB distension, GB wall edema, and collection of pericholecystic fluid were considered as positive signs for ACC presence. The sensitivity of detection of at least one of these criteria in US made up 83.7 % (95 % CI: 75.1 to 89.7 %). The specificity for that circumstance accounted for 47.7 % (95 % CI: 37.6 to 58 %). Perhaps, therefore US might be of limited diagnostic modality for the diagnosis of ACC.

Superb Microvascular Imaging (SMI) technique of Doppler sonography is more highly accurate and sensitive than the traditional Doppler in terms of spotting of blood flow (Yokoe et al, 2018). This special advantage of SMI allows specialists to uncover the increased gallbladder intraluminal flow in patients with ACC. The results of performance, accuracy, and detection quality of color or power Doppler sonography for the diagnosis of ACC is strongly affected by a range of factors including the human (sonographer) factor and the patient's body configuration. This is the biggest barrier for the designation of the SMI technique of Doppler sonography as a standard diagnostic tool for ACC (Yokoe et al, 2018).

Computed Tomography

Although the most common clinical scenarios and the literature suggest that US is the diagnostic method of choice in patients clinically suspected of having acute cholecystitis, it is common practice in many countries with a well-organized healthcare system, for patients with acute abdominal pain and tenderness to undergo contrast-enhanced computed tomography (CT) during the initial work-up. Moreover, CT has been validated for use in the diagnosis of acute cholecystitis according to the Tokyo Guidelines (Hirota et al, 2007). The diagnostic performance of CT in patients with acute cholecystitis was reported by many recent studies as being equivalent to that of US (van Randen et al, 2011; Stoker et al, 2009; Yokoe et al, 2018). Interestingly, Wertz et al. (2018) reported that US sensitivity and CT sensitivity for ACC were not as good as sensitivities reported in prior studies and made up 68% and 85%, respectively. According to those authors, CT was better with higher statistical significance for the diagnosis of ACC than US, the most likely due to an unclear clinical picture, the patient population, and a high proportion of poor-quality US examinations.

On the other hand, a range of occult US results for ACC (nearly 70% of US examinations for ACC were poor in quality) was reported in the study by Wertz et al. (2018). This problem was solved by using a CT scan which was performed the same day. The pericholecystic fluid was observable on CT. This kind of fact leaves the reliability of ubiquitous and easily accessible tools under question.

However, some modes of CT scan can be extremely valuable and indispensable in the diagnosis of ACC, including gallbladder gangrene. Wu et al. (2011) previously reported that 12 (70.6%) of 17 patients with gangrenous cholecystitis had a gallbladder wall perfusion defect (figure 1), and Fuks et al. (2012) reported that no gallbladder wall enhancement was detected in 11 (73.3%) of 15 patients with gangrenous cholecystitis. In the latter study, the surgical decision – indication for open cholecystectomy was made taking into account the lack of gallbladder wall enhancement. Similarly, Chang et al (2016) found

decreased gallbladder wall enhancement contrast-enhanced CT in 70% of patients with gangrenous cholecystitis.

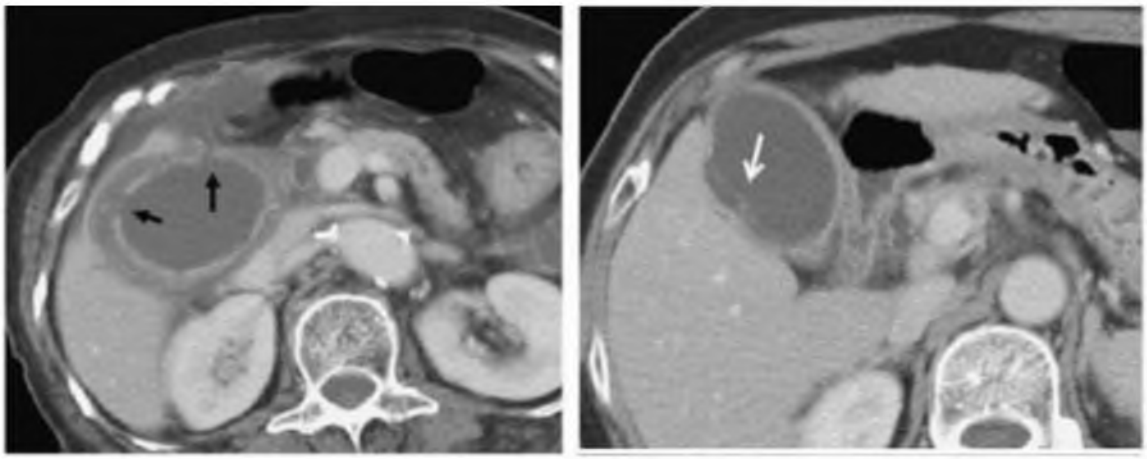

Figure 2. *Axial contrast-enhanced CT image shows discontinuation of the mucosal enhancement with a gap at the gallbladder wall – CT signs of gangrenous cholecystitis (Wu et al, 2010).*

In the TG18, specialists compared the diagnostic accuracy of plain CT with contrast-enhanced CT for ACC. Typical CT images of gangrenous cholecystitis of the woman in her 70s are shown in figure 3a. Enlargement of the gallbladder, thickening of the gallbladder wall, and edematous lesions beneath the gallbladder serosa are evident on plain CT (arrows). On contrast-enhanced CT (b and c), irregularity of the gallbladder wall and the partial lack of contrast enhancement can be seen (arrows) as the characteristic appearance of gangrenous cholecystitis. Transient early liver parenchymal staining (b) and edematous changes of the hepatoduodenal ligament (c, arrowhead) were also evident, suggesting widespread inflammation.

By the authors of one more article that included 26 patients with ACC was made an end that the expansion in the transient focal enhancement of the neighboring tissues of the liver to gallbladder during the arterial phase of dynamic CT was more noteworthy in gangrenous cholecystitis than in the patients with nongangrenous cholecystitis. Along these lines, in patients with suspected acute cholecystitis, performing dynamic CT can be invaluable to guarantee high accuracy in diagnosis and determination of further steps for those with destructive cholecystitis (Maehira et al, 2016). Along these lines, assessing the level of transient focal enhancement of the liver contiguous the gallbladder during the arterial phase of dynamic CT can be a prescient element of difficult laparoscopic cholecystectomy (Maehira et al, 2017). Multivariate analysis of preoperative CT findings showed that the absence of gallbladder wall enhancement (OR 3.15, P =

0.03), presence of a gallstone in the gallbladder infundibulum (OR 2.11, $P = 0.04$), and inflammation of the hepatic pedicle (OR 1.71, $P = 0.04$) were associated with a high rate of conversion in laparoscopic cholecystectomy (Jang et al, 2020).

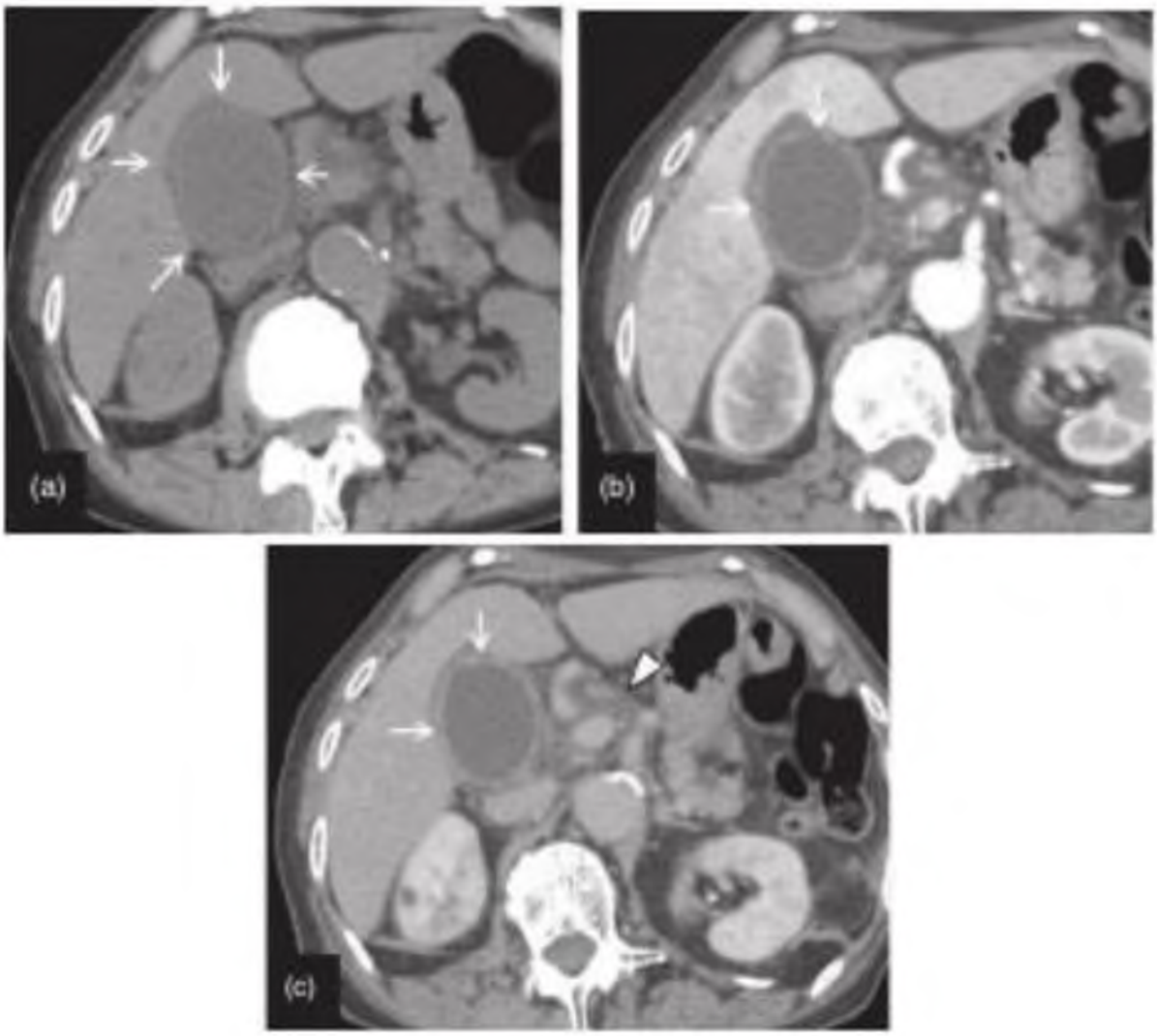

Figure 3. *CT images of gangrenous cholecystitis.* ***a*** *– plain CT;* ***b*** *– dynamic contrast-enhanced CT (early phase);* ***c*** *- dynamic contrast-enhanced CT (equilibrium phase) (Yokoe et al, 2018)*

Magnetic Resonance Imaging

Based on the available literature, summarized estimates of the diagnostic accuracy of MRI are comparable to those of US, making it an imaging modality to consider in patients with technically limited US examinations. In the past, MRI required long examination times, thereby limiting imaging of the abdomen because of respiration and intestinal motility. Because of technical improvements, MRI protocols for patients with acute abdominal pain involve examination times shorter than 15 minutes. Now that MRI has become a fast, safe, and well-tolerated examination, it is anticipated that this modality will become increasingly available

in the emergency setting. MRI has already been introduced for other acute abdominal conditions, such as appendicitis, diverticulitis, and pancreatitis. Further studies with larger sample sizes are needed for more precise estimates of the accuracy of MRI for this indication. (Kiewiet et al, 2012). Evidence of MRI accuracy for ACC is limited due to its high cost and long examination times.

The generally accepted imaging findings of acute cholecystitis are thickening of the gallbladder wall (≥4 mm), enlargement of the gallbladder (long axis ≥8 cm, short-axis ≥4 cm), gallstones or retained debris, fluid accumulation around the gallbladder, and linear shadows in the fatty tissue around the gallbladder (Fuks et al, 2012). A 2012 meta-analysis of the magnetic resonance imaging (MRI) diagnosis of acute cholecystitis conducted by Kieiwiet et al (2012) included three studies on MRI including a total of 131 patients. MRI sensitivity ranged from 50% to 91%, with specificities from 78% to 89%. Summary sensitivity was 85 % and specificity was 81 %. Even contrast-enhanced MRI modalities granted almost the same results for ACC diagnosis. Namely, transient enhancement of pericholecystic hepatic parenchyma on immediate postgadolinium SGE images was seen in 7 of 10 patients with acute cholecystitis, and not observed in other patients (Loud et al, 1996). Therefore, contrast-enhanced MRI was recommended for patients under suspicion of gangrenous cholecystitis by TG18 (Yokoe et al, 2018).

Even non-contrast MRI/MRCP (Magnetic Resonance Cholangiopancreatography) provides a good visualization of thickening of the gallbladder wall, fluid retention around the gallbladder wall, and enlargement of the gallbladder, and one study has found that it is not inferior to contrast-enhanced MRI (Oh et al, 2003). The anatomy of the biliary system is easy to assess on MRCP (by the visualization of accessory hepatic ducts and the common bile duct), making it useful for preoperative investigation. In terms of differentiation from chronic cholecystitis, thickening of the gallbladder wall and dense staining of the gallbladder bed in the early phase of contrast-enhanced MRI have been found to have 92% specificity for the diagnosis of acute cholecystitis (Yokoe et al, 2017).

In general, the diagnostic accuracy of MRI might be comparable to that of AUS, insufficient data are available to support it. (Ansaloni et al, 2016). However, MRI is more suitable and informative for the detection of choledocholithiasis.

Laboratory tests

As usual, elevated white blood cells (WBC) count and the level of C-reactive protein are associated with any inflammatory process. These phenomena are also characteristic of ACC. In fact, WBC count and CRP with fever were considered as one out of three diagnostic criteria for ACC by TG07 (Hirota et al, 2007). The correlation between an increase in the level of CRP and an increase in the severity

of acute cholecystitis is higher than 75% (Kabul Gurbulak et al, 2015). Likely, Bouassida et al. (2020) report that C-reactive protein was the unique inflammatory marker for the prediction of advanced acute calculous cholecystitis progression as well as conversion from laparoscopic cholecystectomy to open surgery. In that research, this marker was associated with the highest discriminative evidence in the diagnostics of the advanced form of ACC reflecting a satisfactory sensitivity of slightly more than 70% and specificity up to 71%. The risk of conversion was also clearly predictable due to the elevated CRP level compared to other inflammation mediators involved in the research.

However, the specificity and sensitivity of these blood tests are still widely controversial. In the laboratory features, Asiltürk Lülleci et al. (2016) found differences in systemic inflammatory markers between elderly and nonelderly patients. Elderly patients had significantly higher CRP values than patients under 65. In addition, while 41.2% of elderly patients had an elevated WBC count, 26.4% of nonelderly patients had an increased WBC count. Similarly, in the patient population of the research conducted by Parker et al. (1997), 41% of the patients had WBC counts in the normal range, with only a quarter of them having marked leukocytosis.

In a retrospective analysis of 100 patients with acute cholecystitis suspicion who underwent a hepatobiliary scan, Singer and colleagues investigated whether the presence or absence of various clinical or laboratory parameters (including WBC count, total bilirubin, AST, ALT, alkaline phosphatase, and amylase) would identify patients at high risk for having a positive hepatobiliary scan which means acute inflammation process in the gallbladder. None of the laboratory values evaluated in this study were predictive of having a positive hepatobiliary scan (Singer et al, 1996).

A study of 311 patients admitted with suspected acute cholecystitis described the relationship between elevated liver function tests (LFTs) (specifically bilirubin, ALT, and alkaline phosphatase) and acute cholecystitis (Dunlop et al, 1989). The incidence of confirmed acute cholecystitis was 73.6%, and though LFT abnormalities were statistically more frequent in patients with acute cholecystitis than without acute cholecystitis, these results were not clinically useful because of the broad overlap of values in those with other clinical conditions associated with abdominal pathology. Furthermore, normal LFTs did not exclude cholecystitis. Routine laboratory tests are adjunct to the workup of patients with suspected acute cholecystitis, but ultimately more specific laboratory tests, clinical pictures, and up-to-date imaging studies are needed for accurate diagnosis.

CONCLUSIONS

Accurate diagnosis of ACC, especially severe forms of this pathology is extremely important in surgical practice. We reviewed a variety of methods for investigating patients with ACC. Most of these modalities are mentioned in popular guidelines like TG and WSES. While the TG and WSES have certainly improved the understanding of ACC, some criticisms still have followed. There are some ambiguities in terms of timing and the type of surgery for certain morphologic forms of ACC. It is all-known fact that these obscurities demand point-by-point diagnostic modalities to be solved.

Namely, because of the poor diagnostic performance of AUS in the diagnosis of ACC, diagnostic accuracy of other imaging modalities must be assessed. Contrast-enhanced CT and MRI could be a reasonable choice for a more accurate diagnosis and making a surgical decision for destructive forms of ACC.

Recently, many laboratory tests have been developed to disclose the character and outcomes of inflammation processes. These advances might be a good alternative and/or supplement to the diagnostic arsenal for ACC.

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