Role of Procalcitonin in diagnosis of bacterial infection after percutaneous ablation therapy for HCC patients

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most common primary liver malignancy which represents up to 90% of the total primary liver cancers. Procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally the levels of it correlate with the degree of sepsis. **Objectives:** This study aimed to determine the role of procalcitonin to predict bacterial infection and correspondingly the usefulness of antibiotic use in HCC patients who develop fever after TACE, PET or RFA. **Summary**: Trans-arterial chemoembolisation (TACE) became the treatment of choice for multinodular hepatocellular carcinoma. The use of prophylactic antibiotics following intervention is controversial; Procalcitonin seems to be a promising marker for diagnosis of sepsis in TACE treated HCC patients to optimize the unnecessary use of antibiotics.

Keywords: **Predictive; Procalcitonin; Bacterial Infection; Hepato –Cellular Carcinoma; Ablation Therapy.**
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Introduction

The most globally used primary treatments for unresectable hepatocellular carcinoma (HCC) are transarterial chemoembolization (TACE), percutaneous ethanol injection (PET) and radiofrequency ablation (RFA) **(1).** These procedures have low rate of major complications (4–7% in TACE and 2-3% in RFA) such as liver infarction, acute hepatic failure, intrahepatic biloma, hepatic abscess and cholecystitis (**2**) so they are generally well tolerated **(3).**

Postablation syndrome pathogenesis is still unclear. In most patients, the etiology of fever after these maneuvers denotes the underlying extensive necrosis of the tumor and healthy cells. Infectious complications are very rare after these procedures**.** Whatever the cause might be, fever causes concern and frequently leads physicians to prescribe unnecessary antibiotics. The concern of physicians is usually based on the fact that baseline cirrhosis of HCC patients is an independent risk factor for sepsis and a poor outcome of infectious complications **(4).**

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin and it arises once preprocalcitonin is cleaved by endopeptidase. It is composed of 116 amino acids and is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine **(5).**

The diagnostic value of PCT to predict bacterial infection has been studied in various diseases and patient groups **(6).** Procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally the levels of it correlate with the degree of sepsis. PCT has sensitivity (85%) and specificity (91%) for differentiating patients with systemic inflammatory response

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syndrome (SIRS) from those with sepsis, when compared with IL-2, IL-6, IL-8, CRP and TNF alpha (**7**).

This study aimed to determine the role of procalcitonin to predict bacterial infection and correspondingly the usefulness of antibiotic use in HCC patients who develop fever after TACE, PET or RFA.

HEPATOCELLULAR CARCINOMA

EPIDEMIOLOGY

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy which represent up to 90% of the total primary liver cancers. Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths worldwide, after lung, colorectal, and stomach cancer **(8)**.

In Egypt, it represents the fourth common cancer**.** Egypt ranks the third and 15th most populous country in Africa and worldwide, respectively. In Egypt, the health authorities consider HCC as the most challenging health problem **(9)**.

Risk factors

Risk factors for HCC can be divided to Environmental-related risk factors which including infectious risk factor (mainly hepatitis B and hepatitis C viral infections) and noninfectious risk factors (mainly chemical compounds, alcohol and cigerate smoking). Also there are host/ genetic related risk factors.

Cirrhosis

Cirrhosis remain the most important risk factors for the development of HCC and up to 90% of HCC occur on top of liver cirrhosis of which viral hepatitis and excessive alcohol intake are the leading risk factors worldwide **(Bruix and Sherman., 2010)**

Viral hepatitis

Hepatitis B and C considered of the most common causes of chronic hepatitis in the world.

Hepatitis B virus (HBV)

Hepatitis B virus (HBV) is a double-stranded, circular DNA molecule with eight genotypes (A to H). Genotypes A and D are more common in Europe and the Middle East, while genotypes B and C are more common in Asia **(10).**

Several epidemiological studies have demonstrated significant hepato-carcinogenicity with chronic HBV infection. Unlike other causes of chronic hepatitis, HBV is unique in that HCC can develop without evidence of cirrhosis. Worldwide, HBV accounts for 88% of cirrhosis-related HCC **(11).**

Genotype C has been associated with a higher risk of HCC than genotypes A, B, and D, also HBV DNA levels >10^5/mL viral copies is associated with a 3 times increased risk of developing HCC in 8–10 years follow-up **(12)**. Hepatitis B surface antigen (HBsAg) is hematological marker that carries a significant risk for development of HCC however; Patients with positive hepatitis B core antibody (anti-HBc) with HBsAg-negative marker also remain at risk for development of HCC **(13).**

Hepatitis C virus (HCV)

Hepatitis C virus (HCV) is a small, single-stranded RNA virus, which exhibits high genetic variability. There are six different genotypes of HCV isolated. Genotypes I, II, and III are predominant in the Western countries and the Far East, while type IV is predominant in the Middle East. Once infected with HCV, 80% of patients progress to chronic hepatitis, with ~20% developing cirrhosis **(14).**

The risk of HCC is reduced significantly in patients who obtained a sustained viral response after treatment of HCV with reduction in all-cause mortality. While advances in medications recently have made treating HCV easier, vaccinations against the virus remain elusive **(15).**

Toxins

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Aflatoxin produced by Aspergillus species (molds) found on grains, corn, peanuts, or soybeans stored in warm humid conditions is a potent hepatocarcinogen. The risk of HCC with aflatoxin is dependent on the dose and duration of exposure. Aflatoxin exerts a synergistic effect on hepatitis B- and C-induced liver cancer, the risk being 30 times greater with chronic hepatitis B plus aflatoxin exposure than with aflatoxin exposure alone **(16).**

Screening

Surveillance for at risk people for early detection of HCC should have the goal of decreasing mortality and improving patient outcomes. The prognosis for HCC is driven by the tumor stage, with curative options providing a 5- year survival exceeding 70% for early-stage HCC compared with a median survival of ~1–1.5 years for symptomatic advanced- stage cases treated with systemic therapies. Thus, professional societies recommend HCC surveillance in high- risk individuals, including those with cirrhosis and subgroups of patients with chronic HBV infection. Guidelines across scientific societies coincide that screening for HCC should be performed semi- annually as a 6- month interval yields improved survival compared with annual surveillance and non- inferior outcomes compared with a 3- month interval **(17).**

Screening modalities

Modalities available for HCC screening include both radiographic tests and serological markers.

Radiological tests

Ultrasonography (US)

Sensitivity of US imaging is variable, ranging from 35% to 84% and is operator and equipment dependent; however, studies have reported a specificity >90% when used for screening. Small HCC nodules ≤2 cm represented 85% of the lesions that failed to be detected by US **(18).**

Multiphase computerized tomography (CT) and magnetic resonance imaging (MRI) with contrast

HCC lesions exhibit increased arterialization as well as decreased presence of contrast agents during the portal phase of imaging (washout) on both CT and MRI scans. Tumors ≥2 cm are detected by CT and MRI at 90% sensitivity, while sensitivity detection of tumors between 1 and 2 cm is 65% and 80%–92% and that for tumors <1 cm is 10% and 34%–71%, respectively. CT and MRI are preferred in patients who have equivocal results utilizing US as their initial modality **(19)**.

AFP sensitivity is lower with small HCC lesions. It can be elevated in acute hepatitis, cirrhosis, colitis, germ cell tumors, and intrahepatic cholangiocarcinoma. AFP levels above 400 ng/mL predict for HCC with specificity more than 95%, but sensitivity is lower at this higher cutoff value. In 2004, **Lin et al., (20)** demonstrated that surveillance with AFP and ultrasound was cost-effective regardless of the incidence of HCC**.**

The highest accuracy for diagnosing HCC occurs when all three markers with appropriate cutoff values are used together. A DCP >40 mAU/mL + AFP >20 ng/mL and AFP-L3 >10% yield a sensitivity of 82.2% with a specificity of 82.4**% (21).**

Diagnosis

Early diagnosis of HCC is very important to provide best treatment results. Chronic hepatitis leads to the development of cirrhosis. Cirrhotic livers exhibit regenerative nodules, which result from increased proliferation of hepatocytes and between these regenerative nodules HCC can vary based on the size of the nodules **(22)**.

Diagnostic modalities

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Imaging

Nodules <1 cm detected via US that cannot be defined should be followed up with a repeat US in 3–4 months. Nodules >1 cm detected via US should have further radiologic investigation including either contrast-enhanced triple or quadriphasic CT or MRI **(23).**

Although most HCCs have characteristic features in imaging, ~10% of the tumors (but up to 30% of tumors 1–2 cm in diameter) have an atypical presentation, lacking the imaging hallmarks of HCC. The International Consensus Group for Hepatocellular Neoplasia has proposed major histological features of HCC, which include stromal invasion, increased cell density, intratumoural portal tracts, unpaired arteries, pseudo-glandular pattern and diffuse fatty changes (**24)**.

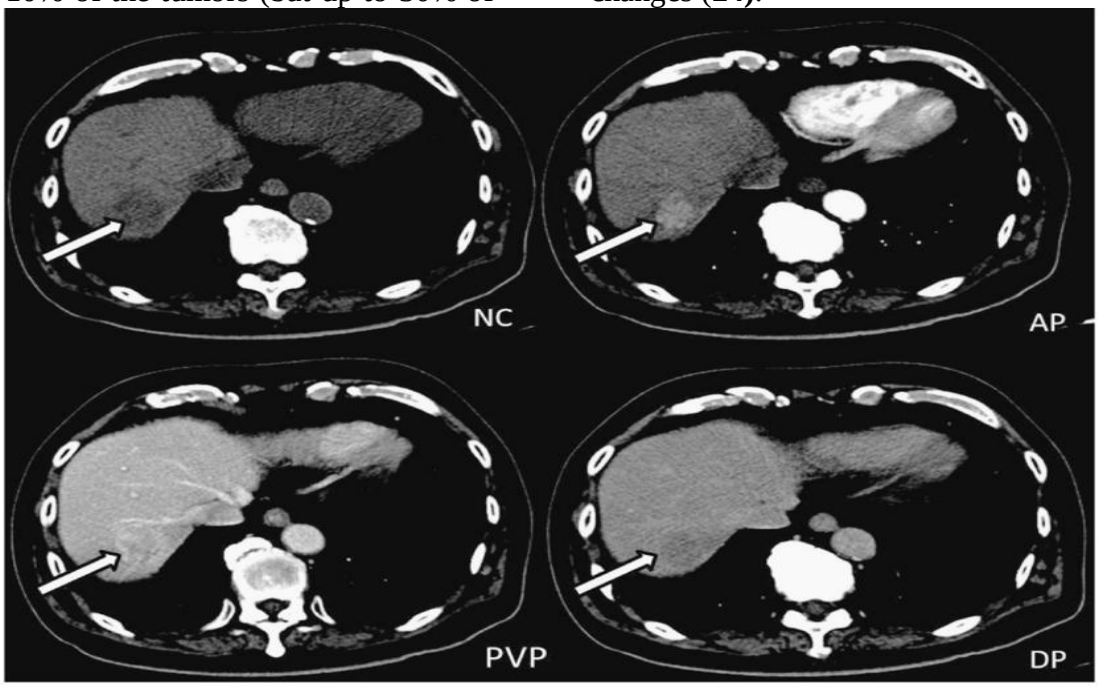

Figure (1): Quadriphasic images of the enhancement features in a typical HCC (arrows) demonstrating hypo-attenuation on noncontrast (NC), hyperenhancement on arterial phase (AP) and washout on portal venous phase (PVP) and delayed phase (DP)

Staging

Stratification of patients diagnosed with HCC into groups is the primary aim of staging systems. Staging systems will assist in organizing patients into groups based on prognosis and can guide clinicians in a choice of therapy, aid patient counseling and facilitate patient selection and randomization for research protocols **(25).**

In 2010, the AASLD published their recommendations regarding staging systems for HCC. Staging systems should best assess the prognosis of HCC in that a staging system should take into account tumor stage, liver function, and physical status. BCLC is the only system that takes into account all of these factors **(26).**

Surgical approaches

Resection

Surgical resection is the accepted treatment of choice for non -cirrhotic patients and offers the best curative rate with a 5-year survival of 41%–74%. The resectability of the tumor is dependent on the tumor size, location, underlying liver function and whether or not the remaining liver volume will allow for resection without significantly increasing post-resection morbidity and mortality. The candidates for this therapy are patients with a solitary tumor confined to the liver, no radiologic evidence of

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vascular invasion, and well-maintained liver function **(27)**.

In patients with normal synthetic function, the size of the tumor does not necessarily affect the outcome when residual volume (volume of remaining liver) is adequate and technical aspects of the surgery are achievable. Utilizing the MELD, a score of ≤ 8 has been shown to have no mortality as compared to a perioperative mortality of 29% for a score of >9.95 **(28)**

Perioperative portal vein embolization (PVE) is a technique utilized to cause hypertrophy of the anticipated residual liver remnant, thus permitting a more extensive liver resection. When PVE is performed, an overall increase in the liver volume of 10%–12% can be achieved. Perioperative PVE has less major complications compared to patients who have had major resection without PVE **(29).**

Liver transplantation

Orthotopic liver transplantation (OLT) is the best curative option for patients with decompensated cirrhosis, and HCC is a solid cancer that can be treated with transplantation**.** **Mazzaferro et al., (30)** published a landmark study with <50 patients who were transplanted for HCC with specific criteria, which became known as the Milan criteria. These specific criteria included (1) single tumor diameter less than 5 cm (2) not more than three foci of tumor, each one not exceeding 3 cm (3) no angioinvasion (4) no extrahepatic involvement. Since the introduction of these criteria, long-term recurrence-free survival after liver transplantation in adults with HCC improved from 30% to 75% .A systemic review of 90 studies that followed 17,780 patients over a 15-year period identified the Milan criteria as an independent prognostic factor of outcome after OLT **(30).**

Locoregional therapies have been used to downsize patients with HCC exceeding current transplant criteria with the goal to decrease the tumor burden in order to meet transplant criteria. **Yao et al, (31)** published a down staging protocol consisting of transarterial chemoembolization (TACE) and/or radiofrequency ablation (RFA) and demonstrated survival rates of 96.2% at 1 year and 92.1% at 4 years among patients who received transplantation. Post-transplant survival data are comparable in patients who underwent downsizing with those within conventional criteria **(31).** Ablative therapies can also be used as bridging therapies for transplantation, deceleration of tumor progression, minimization of dropout and improvement of post-transplant survival **(32).**

Nonsurgical approaches

Local ablation is considered a potentially curative therapy of small size HCC, generally <3–4 cm. Tumor destruction can be achieved with chemicals, such as percutaneous ethanol injection (PEI) or thermal ablation, which includes RFA, MWA, cryoablation and laser interstitial thermotherapy (LITT) **(23).**

Transarterial chemoembolization (TACE)

The most commonly used initial treatment for locoregional HCC as well as for downstaging tumors that exceed criteria is TACE. TACE can also be considered as neoadjuvant therapy to either reduce tumor volume or even target micrometastasis **(33).**

This tumor characteristic provides the pathologic basis for the radiologic features used to diagnose HCC. Embolization of the hepatic artery branch leads to selective tumor hypoxia and eventually tumor necrosis. This is accomplished by a significant reduction in arterial blood flow through the use of image-guided catheter-based infusion of particles **(34)**. Prior to arterial embolization, a chemotherapeutic agent is injected. Several chemotherapeutic agents have

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been historically used, including doxorubicin, cisplatin, mitomycin, and epirubicin **(35)**.

Contraindications for TACE are decompensating cirrhosis (Child–Pugh B), massive tumor with extensive replacement of lobes, severely reduced portal flow and a creatinine clearance of <30 mL/min **(36)**.

Liovet et al, (37) found that survival probabilities for TACE were 82% and 63% for 1 and 2 years, respectively, for unresectable HCC. The response to TACE is an independent predictor of survival. Additional studies have shown an improvement in survival in TACE-treated patients in the range of 20%–60% at 2 years. Morbidity with embolization is relatively low (<5%) and common complications include abdominal pain, nausea, ileus and fever, which are consistent with post-embolization syndrome.

Transartetial radiation

Transartetial radio-embolization is a form of catheter-directed internal radiation that delivers small microspheres with radioisotopes directly into the tumor. Yttrium-90 (Y-90) microspheres or iodine-131-labeled lipiodol 127 are administered in a procedure similar to TACE. This procedure has been shown to be safe and effective in cirrhotic patients with HCC **(38).**

A pretreatment evaluation that often includes an arteriogram, superior mesenteric angiogram, and celiac trunk angiogram is necessary to evaluate for the presence of arterio-portal shunting. Coil embolization of these collateral vessels may be necessary to decrease unintended deposition of microspheres outside the targeted area. Vessels most often embolized include the inferior esophageal, left inferior phrenic, accessory left gastric, supraduodenal, and retroduodenal arteries **(38).**

Y-90 is contraindicated in patients with hepato -pulmonary shunting, which can lead to extremely high levels of pulmonary radiation exposure and the development of radiation pneumonitis. The reported rate of complete tumor necrosis in patients with tumors <3 cm was 90%. The 2010 AASLD clinical practice guidelines stated that radio-embolization with Y-90 glass beads has been shown to induce extensive tumor necrosis with an acceptable safety profile; however, no studies demonstrating an impact on survival have been established **(26).**

Percutaneous local ablation

Percutaneous local ablation, which includes both radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), is the standard of care for BCLC stage 0-A HCC not suitable for surgery **(39).**

Radiofrequency ablation (RFA)

RFA is the treatment of choice for local destruction of liver tumors. RFA produces coagulative necrosis of the tumor while leaving a safety margin around the tumor, leading this to be the most common local ablative therapy. RFA can be performed both percutaneously under radiological guidance using CT or US and during surgery guided by intraoperative US. Complete ablation of tumors <2 cm is possible in >90% of cases **(40)**.

Percutaneous ethanol injection (PEI)

Ethanol injection requires multiple injections on separate days and rarely induces significant necrosis in tumors >3 cm largely because the injected ethanol rarely reaches the entire tumor volume. Tumor necrosis rates are 90%–100% for tumors <2 cm, 70% for 2 -3 cm tumors, and 50% in HCC tumors between 3 and 5 cm. In one prospective nonrandomized study, RFA achieved higher ablation rates on HCC tumors <3 cm than percutaneous ethanol injection (90% vs 80%) with fewer treatments **(41).**

Microwave ablation

Microwave ablation (MWA) can be utilized both percutaneously and intra-operatively and is a potentially curative

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ablative procedure. It is a method very similar to RFA, except MWA utilizes electromagnetic waves with frequencies >900 kHz to irradiate and ablate tumor foci.

Earlier studies comparing MWA and RFA demonstrated no statistical difference in efficiency, and more recent studies using improved MWA modalities show potential. Clinical advantage of MWA over RFA and its potential to demonstrate increased rates of tumor necrosis with a reduction in overall treatments need to be evaluated **(42).**

Complications of locoregional therapy

Major complications have been consistently low and have been reported at a rate up to 5.7% **(43**).

Post-ablation syndrome

Post-ablation syndrome occurs from 24 to 48 hours following ablation and lasts no longer than 10 days. It is believed to occur following cytokine release and tumor necrosis, causing patient fever and flu-like symptoms. If symptoms persist following 10 days after the procedure, alternate diagnoses should be considered and acute infection should be ruled out **(44)**.

PROCALCITONIN

Procalcitonin (**PCT**) is a peptide precursor of the hormone calcitonin, the latter being involved with calcium homeostasis**.** It was first identified by Leonard J. Deftos and Bernard A. Roos in the 1970s. It is composed of 116 amino acids and is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine **(45).**

During inflammation, lipopolysaccharides (LPS), microbial toxin, and inflammatory mediators, such as interleukin 6 (IL-6) or tumor necrosis factor alpha (TNF-α), induce the CALC-1 gene in adipoctyes, but PCT never gets cleaved to produce CT. In a healthy individual, PCT in endocrine cells is produced by CALC-1 by elevated calcium levels, glucocorticoids, calcitonin gene related peptide (CGRP), glucagon, or gastrin and is cleaved to form CT, which is released to the blood **(46)**.

In healthy and non-infected individuals, transcription of PCT only occurs in neuroendocrine tissue, except for the C cells in the thyroid. The formed PCT then undergoes post-translational modifications, resulting in the production small peptides and mature CT by removal of the C-terminal glycine from the immature CT by peptidylglycine α-amidating monooxygenase (PAM) (**47).**

In a microbial infected individual, non-neuroendocrine tissue also secretes PCT by expression of CALC-1. A microbial infection induces a substantial increase in the expression of CALC-1, leading to the production of PCT in all differentiated cell types. The function of PCT synthesized in non-neuroendocrine tissue due to a microbial infection is currently unknown, but, its detection aids in the differentiation of inflammatory process **(47).**

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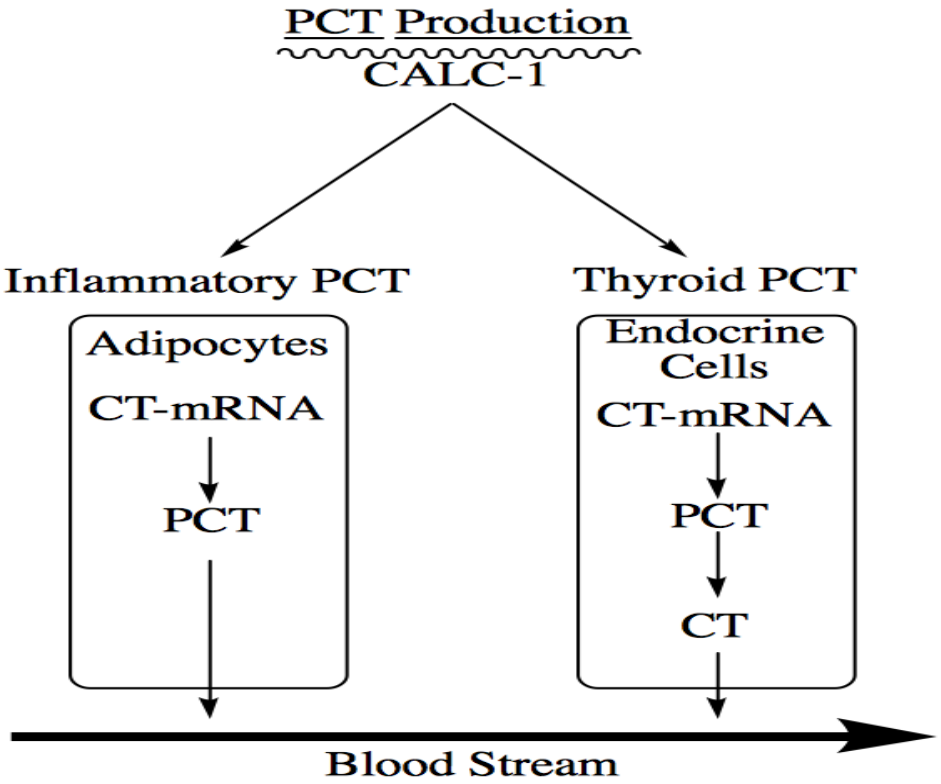

Figure (2): Production pathway of PCT and CT in healthy and infected individuals via the induction of CALC-1 gene

Emerging bacterial resistance to antimicrobial therapeutics calls for more strict efforts to reduce antibiotic overuse. Towards this aim, there has been considerable interest in antibiotic stewardship programs aimed at reducing antibiotic overuse by tailoring antibiotic therapy to individual needs of patients **(48).**

Despite the successful implementation of diagnostic biomarkers in different fields of medicine (for example, D-dimers in pulmonary embolism, natriuretic peptides in acute heart failure, troponin in myocardial infarction), accurate and timely diagnosis of bacterial infections remains a challenge **(49).**

In this diagnostic dilemma, procalcitonin (PCT) has stimulated great interest as a potentially more specific marker for bacterial infection. PCT is produced in response to endotoxin or mediators released in response to bacterial infections (that is, interleukin (IL)-1b, tumor necrosis factor (TNF)-a, and IL-6) and strongly correlates with extent and severity of bacterial infections**.** Because up-regulation of PCT is attenuated by interferon (INF)-g, a cytokine released in response to viral infections, PCT is more specific for bacterial infections and may help to distinguish bacterial infections from viral illnesses **(50).**

Measurement of procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis, although levels of procalcitonin in the blood are very low. PCT has the greatest sensitivity (90%) and specificity (91%) for differentiating patients with systemic inflammatory response syndrome (SIRS) from those with sepsis, when compared with IL-2, IL-6, IL-8, CRP and TNF-alpha **(7).**

Evidence is emerging that procalcitonin levels can reduce unnecessary antibiotic prescribing to people with lower respiratory tract infections. Currently, procalcitonin assays are widely used in the clinical environment and meta-analysis

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reported a sensitivity of 76% and specificity of 70% for bacteremia **(51).**
A systematic review comparing PCT and C-reactive protein (CRP) found PCT to have a sensitivity of 80% and a specificity of 77% in identifying septic patients. In a study done by Tan et al, PCT outperformed CRP in diagnostic accuracy of predicting sepsis **(52).**
Percutaneous ablation therapy is generally well-tolerated procedures for treating HCC. However, a considerable number of patients experience the postembolization or postablation syndrome, which is a transient self-limiting complex of symptoms or signs of fever and general malaise (**2).**
Fever after percutaneous ablation therapy was observed in 17.2% of patients. Even though the actual incidence of bacterial infection in patients undergoing these procedures is quite low (0.8–2.5%), fever always causes a concern for infectious complications frequently leading physicians to prescribe unnecessary antibiotics **(53).**
PCT might be a biomarker to detect infectious complications after percutaneous ablation therapy in HCC patients, if there is clinical suspicion of infection. PCT-guided antibiotic treatment could contribute to reduce unnecessary use of antibiotics without worsening outcomes in patients with fever after percutaneous ablation therapy **(54).**
The level of procalcitonin in the blood stream of healthy individuals is below the limit of detection (0.01µg/L). The level of procalcitonin rises in a response to a pro-inflammatory stimulus, especially of bacterial origin. It is therefore often classed as an acute phase reactant (**55)**
The induction period for procalcitonin ranges from 4–12 hours with a half-life from 22–35 hours. It does not rise significantly with viral or non-infectious inflammations. In the case of virus infections this is due to the fact that one of the cellular responses to a viral infection is to produce interferon γ, which also inhibits the initial formation of procalcitonin **(56).**
With the inflammatory cascade and systemic response that a severe infection brings, the blood levels of procalcitonin may rise multiple orders of magnitude with higher values correlating with more severe disease. Remarkably the high procalcitonin levels produced during infections are not followed by a parallel increase in calcitonin or a decrease in serum calcium levels **(57).**
Finally Due to PCT level variance between microbial infections and healthy individuals, it has become a marker to improve identification of bacterial infection and guide antibiotic therapy **(5).**

Summary:
Trans-arterial chemoembolisation (TACE) became the treatment of choice for multinodular hepatocellular carcinoma. The use of prophylactic antibiotics following intervention is controversial; Procalcitonin seems to be a promising marker for diagnosis of sepsis in TACE treated HCC patients to optimize the unnecessary use of antibiotics.

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