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REVIEW

Use of procalcitonin in clinical oncology: a literature review

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SUMMARY

The use of procalcitonin (PCT) as an early marker of infectious episodes in cancer patients is still controversial. We performed a MEDLINE search of peer-reviewed articles published between January 1990 and December 2015, and finally we analysed 15 articles.
PCT seems to have a good diagnostic value of infectious episodes in cancer patients and its accuracy seems greater if we consider major events, such as bloodstream infections and sepsis. Serial evaluations of this protein seem to be more accurate in the diagnostic phase and useful to predict outcome and response to antibacterial treatment. On the other hand, some issues have yet to be solved, such as the use of a validated method of determination, the definition of a standard cut-off, and the heterogeneity among different settings of patients (e.g. early versus advanced-stage cancer, or haematological versus solid tumours).
However, it is credible to think that PCT use in everyday clinical practice, preferably in combination with other clinical or laboratory tests, might be of help in finding and detecting early infectious complications in cancer patients.

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INTRODUCTION

In cancer patients it is common to diagnose neutropenia (defined in the consensus guidelines of the Immunocompromised Host Society [IHS] (Hughes 1990) as a neutrophil count of 500 cells/mm^3 or less or a count of <1,000 cells/mm^3 with a predicted decrease to <500 cells/mm^3), which can be correlated either to the malignant neoplasm itself or to antineoplastic chemotherapy.
The Common Toxicity Criteria of Adverse Events of the National Cancer Institute (CTCAE-NCI, version 4.03) delineates neutropenia into four grades following the absolute neutrophil count (ANC):

- grade 1: ANC from 1.5 to 2 x 10^9/L,
- grade 2: ANC from 1 to 1.5 x 10^9/L,
- grade 3: ANC from 0.5 to 1 x 10^9/L,
- grade 4: ANC below 0.5 x 10^9/L.

Neutropenia is often complicated with fever: such condition is commonly known as febrile neutropenia (FN), defined as an oral temperature >38.5°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count <0.5 x 10^9/L, or expected to fall below 0.5 x 10^9/L.
Medical oncologists' attention is mainly focused on chemotherapy-induced neutropenia and FN. Chemotherapy-induced neutropenia (CIN) and chemotherapy-induced febrile neutropenia (CIFN) are conditions of neutropenia and FN respectively, whose primary cause is the administration of anti-cancer drugs (the time of onset of neutropenia and FN is the main factor that can be used to value such connection). They are the most serious haematological toxicities of cancer chemotherapy and they stand among the main mortality causes in cancer patients.
Neutropenia and FN are common in cancer patients because of several risk factors that can be either due to the patient's characteristics, to the disease itself or to the treatments.
Table 1 shows the principal risk factors associated with the development of FN (adapted from Danova 2015).
Considering the different chemotherapy regimens, certain therapy regimens are associated with a high risk of neutropenia and FN (i.e., a ≥20% risk of developing FN). These include schemes used in several malignancies, reported in *Table 2*.
Other drugs used in cancer treatment are associated with high risk of neutropenia and FN because of their mechanism of action. These include:

- bortezomib, used in the treatment of multiple myeloma, that inhibits the proteasome, permitting the activation of programmed cell death in neoplastic cells, but also in myeloid normal cells;
- alemtuzumab, monoclonal antibody anti-CD52, used against B-cell chronic lymphatic leukemia, which acts against both malignant and normal B and T lymphocytes;
- rituximab, monoclonal antibody anti-CD20, used in the treatment of several non-Hodgkin lymphomas;
- corticosteroids, because of their immunosuppressive effects.

Key words:
Cancer patients, Procalcitonin, Infections, Chemotherapy-induced neutropenia, Febrile neutropenia, Biomarkers of infection.

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Table 1 - *Febrile neutropenia risk factors.*

Class	*Risk Factors*
Patient-related	• Age > 65 • Female sex • Low Performance Status (ECOG ≥ 2) • Low nutritional status • Immunodepression (e.g. HIV infection) • Pre-existing neutropenia or lymphopenia • Open wounds • Active tissue infections • Comorbidity (CV diseases, COPD, liver diseases, diabetes mellitus, anemia)
Disease-related	• Type of tumour (haematological vs solid) • Bone marrow metastases • Advanced/Refractory disease • LDH high levels (e.g. lymphoma)
Treatment-related	• Chemotherapy regimen • Relative Dose Intensity (RDI) • Previous chemotherapy regimens • Concomitant or previous radiation therapy on bone marrow (≥20%) • Complicated neutropenia in previous cycle (prolonged FN, hypotension, sepsis, pneumonia or fungal infection) • CT delay • Previous dose reduction

Table 2 - *Regimens associated with a 20% risk of febrile neutropenia (adapted from Crawford et al 2010).*

Malignancies	*Regimens*
Bladder Cancer	MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) TC (paclitaxel, cisplatin)
Breast Cancer	TAC (docetaxel, doxorubicin, cyclophosphamide) Dose-dense AC/T (doxorubicin, cyclophosphamide, paclitaxel)
Cervix Cancer	TC (paclitaxel, cisplatin)
Gastric Cancer	DCF (docetaxel, cisplatin, fluorouracil)
Head & Neck Cancer	Paclitaxel, ifosfamide, mesna, cisplatin
Non-Hodgkin Lymphoma	CHOP-14, ICE, RICE, DHAP (dexamethasone, cisplatin, cytarabine)
NSCLC	DP (docetaxel, carboplatin)
Ovarian Cancer	Topotecan
Sarcoma	MAID (mesna, doxorubicin, ifosfamide, etoposide) AI (doxorubicin, ifosfamide)
SCLC	CAE (cyclophosphamide, doxorubicin, etoposide) Topotecan
Testicular Cancer	VIP (vinblastine, ifosfamide, cisplatin) BEP (bleomycin, etoposide, cisplatin)

Neutropenia and FN (including CIN and CIFN) are associated with a higher risk of infections (Pizzo 1993). Infectious episodes are quite common among cancer patients. Considering cancer patients being admitted to an acute palliative care medicine unit, almost 40% of them have an infection and 15 to 20% of them develop a polymicrobial infection (Homsi 2000). Furthermore, it is estimated that almost 50% of patients with solid tumours and 60% of patients haematological malignancies die from infectious complications (Zembower 2014).

As far as pathogens are concerned, patients with haematological malignancies are mainly infected by Gram-negative bacilli (such as *E. coli, Klebsiella* spp., and *P. aeruginosa*). However, in the last few decades Gram-positive, mainly staphylococci and streptococci, and polymicrobial infections have become more and more frequent. Gram-positive infections are also the most frequent infectious complications in patients with solid tumours. In recent years an emergency has arisen: many unusual pathogens have been isolated in immunocompromised cancer patients; this represents a continuous challenge for infectivologists and medical oncologists (Pizzo 1993). The risk of infection is even higher, if we consider patients with FN, even if fever is neither specific for infection nor is it pathognomonic of any particular kind of infection (Sharma 2005).

Infections in cancer patients lead to a real reduction of efficacy of anti-neoplastic treatments because of dose reductions and delays in drug administration. Furthermore, treatment of infections requires high economic costs (because of the need for antimicrobial drugs and hospital admission).

These aspects considered, on the one hand, it becomes clear that the best approach to this matter is to prevent infections. This can be done by implementing an optimal prophylaxis in patients at higher risk of neutropenia and FN (that includes hygiene recommendations and the correct use of hematopoietic growth factors and prophylactic antimicrobial therapies). On the other, since it is unlikely to abate the risk of infections in cancer patients, an early diagnosis of infectious complications is extremely important.

Infection in neutropenic patients may be difficult to diagnose and in a high percentage of neutropenic febrile episodes a causative agent cannot be identified. As already stated, a proper diagnosis of an infectious episode is of the utmost importance, since inadequately treated infections may be fatal. Therefore, the possibility to have a specific and rapid marker of infection in these patients is fundamental.

Several markers have been studied as possible early markers of infection in neutropenic oncological patients, such as C-Reactive Protein (CRP), Cluster Differentiation 64 (CD64), proadrenomedullin (Pro-ADM), and PCT. These markers have been previously studied in non-cancer patients.

CRP is widely used as a clinical marker of infection and generally differentiates between viral and bacterial infections. C-Reactive Protein has been studied as a possible marker of inflammation and infection in cancer patients, though different studies have demonstrated that there is no significant difference between the median CRP concentration of oncological patients with infection and the median CRP concentration of oncologic patients without infection (Schüttrumpf 2006).

CD64 is a leukocyte surface antigen, whose upregulation is an early phenomenon in the immune response to bacterial infection.
It has been studied as a potential marker of sepsis or infection in adults, children, and neonates and demonstrated a higher sensitivity and specificity than CRP, white blood cell count, neutrophilic and eosinophilic counts, or ESR in adults. Different studies have been conducted on its use as an early marker of sepsis in cancer patients and it seems that CD64 may be useful to differentiate patients with SIRS (Systemic Inflammatory Response Syndrome) and sepsis (Cid *et al.,* 2010). On the other hand, a recent publication evaluated the expression of CD64 in cancer patients in comparison with healthy subjects and highlighted that patients with advanced cancer, even in the absence of signs of active infection, have higher CD64 expression (Comolli 2015). Therefore, at the moment, the use of CD64 as a marker of sepsis in cancer patients is still to be proven.
Proadrenomedullin is a 185-aminoacid peptide and represents the precursor of adrenomedullin. Its use has been evaluated in different patients (such as cardiac diseases). Recent evidence (Debiane 2014) suggests that it might be highly accurate as an early sepsis biomarker, superior to CRP, especially in critically ill patients.
Procalcitonin is a 116 amino-acid protein with a molecular weight of 13 kDa and is a precursor of calcitonin. A study in 1993 first described its use in the diagnosis of sepsis. Since then, it has been investigated as a marker of bacteremia and sepsis (Simon 2004), but several issues have yet to be resolved.
Firstly, there is no standard procedure for PCT revelation in the patients' serum (different techniques are commercially available and comparisons among them can be difficult). Secondly, no standard cut-off is present to differ among positive and negative results: different studies used different cut-offs, ranging from 0.1 ng/mL to 2 ng/mL. Finally, some studies query its efficacy as an early marker of infection or sepsis.
PCT's specificity and sensitivity as a marker of infectious episodes in cancer patients have been investigated, but they still need defining and its use in everyday clinical practice is controversial. At the moment, there is no solid evidence of its efficacy in detecting infectious complications in patients with haematological or solid malignancies, especially at an advanced stage or treated with chemotherapy.

MATERIAL AND METHODS

As far as search strategy and selection criteria are concerned, we reviewed peer-reviewed articles with the use of MEDLINE (PubMed). Search terms included: "PCT", biomarkers of infection", "infections in cancer patients", "CIN" and "FN". The search was restricted to papers published between January 1990 and December 2015 in English and either journal articles, editorial reviews or systematic reviews.
Among the 15 studies examined, we collected data regarding inclusion criteria, study design, age group, disease group and study results. We then considered a recent review (Prucha 2015) on sepsis biomarkers which discusses the role of PCT in the general population in order to make a proper comparison between the general population and cancer patients.

RESULTS

General population

When considering the general population, some evidence affirms the role of PCT as a possible early biomarker of infection. Experimental models show that PCT secretion is related to the bacterial endotoxin and its serum levels increases to reach a maximum within 12 to 48 hours after contact with bacterial components.
Evidence shows that PCT has a higher sensitivity and specificity than CRP in sepsis diagnosis, but it does not fulfil the role of an ideal biomarker in the diagnostics of sepsis. In fact, it lacks sensitivity in case of abscesses, fungal infections, and tuberculosis. Furthermore, PCT is not fully specific after surgery or in patients with florid autoimmune disease. Specificity is higher when considering a cut-off of 0.2 ng/mL, but there is no consensus over the cut-off to use in clinical practice.
Its use in therapy decision-making is still uncertain. In 2013 recommendations from an expert panel on the use of PCT for decision-making to start, interrupt or stop antibiotic therapy was published; they considered acute pancreatitis, community-acquired infections of lower respiratory tract, bacterial meningitis and ICU patients with suspected community-acquired infections, and concluded that PCT can be used only in a very few clinical circumstances when deciding about therapy management.

Cancer patients

In cancer patients who develop FN, several studies have been done to identify possible easy-access biomarkers that could help in the early diagnosis of infectious complications. A recent meta-analysis (Wu *et al.,* 2015) evaluated the possible use of different biomarkers, such as CRP, PCT and interleukin-6 (IL-6), in the early diagnosis of severe infection in patients with FN. PCT showed the highest positive likelihood ratio (5.49, CI 4.04-7.45) for bacterial infections, but evidence is still weak and more precise *"ad hoc"* studies should be done to better define its role in everyday clinical practice.

Correlation with infectious episodes

Procalcitonin basal values tend to be higher in patients with FN who are developing infectious episodes, mainly bacterial infections, compared with febrile patients with no signs of infection. Patients with a confirmed infection have a statistically significantly higher value of PCT serum levels than patients who have no clear signs of infection (Schüttrumpf *et al.,* 2006). Such values tend to be higher in patients with infectious episodes of a higher clinical impact, such as bloodstream infections (e.g. bacteremia), SIRS, sepsis, and septic shock (Shomali *et al.,* 2012, Meidani *et al.,* 2013, Ahn *et al.,* 2013, Chaftari *et al.,* 2015). Febrile infectious episodes seem to be associated with higher PCT levels than non-febrile infectious episodes (Chaftari *et al.,* 2015). Furthermore, patients with a culture-documented infection, compared with patients with clinically-suspected infections of fever of unknown origin, show higher values (Jimeno *et al.,* 2004) (*Table 3*).
One analysis investigated 104 patients treated with chemotherapy who developed FN. Considering both median and mean baseline PCT values, there was a statistically significant difference ($p<0.01$) between patients who had a microbiologically-documented infection compared with patients with clinically-diagnosed infections or fever of

Table 3 - *Correlations between PCT values and infections (MDI: microbiologically documented infection; CDI: clinically-diagnosed infection; FUO: fever of unknown origin; BSI: bloodstream infection; LBI: localised bacterial infections; FI: febrile infection).*

Study	*PCT values in setting of patients*	*p-value*
Jimeno *et al.*	MDI > CDI or FUO	<0.01
Schüttrumpf *et al.*	Infection > No infection	-
Shomali *et al.*	BSI > LBI or no infection LBI = no infection SIRS/sepsis > no SIRS/ sepsis	0.048 0.95 0.012 and 0.032
Meidani *et al.*	Sepsis > no sepsis	0.000
Ahn *et al.*	Bacteremia > No bacteremia Septic shock > No septic shock	0.005 <0.001
Chaftari *et al.*	FI > No FI Non-febrile cancer > Non-cancer Bacteremia/sepsis > No MDI (fever)	<0.0001 <0.0001 <0.003

unknown origin (the latter had similar median and mean baseline PCT values) (Jimeno *et al.,* 2004).

In 111 patients with a haemato-oncologic condition with a CPR concentration >8 mg/L that median PCT concentrations were higher in patients with an infection than in patients without an infection (0.5 ng/mL vs 0.1 ng/mL in patients with leukopenia and 1.0 ng/mL vs 0.1 ng/mL in patients without leukopenia) (Schüttrumpf *et al.,* 2006).

Another study focused on 248 non-neutropenic cancer patients with solid or haematological malignancies and fever. Baseline PCT values were significantly higher in patients with bloodstream infections than those with localized bacterial infections (1.06 ng/mL vs 0.30 ng/mL, p=.048) and those without any kind of infection (1.06 ng/mL vs 0.31 ng/mL, p=.011). On the other hand, there was no significant difference between patients with localised bacterial infections and those with no microbiological evidence of infection (p=.95). Analysing patients with SIRS or sepsis, it was observed that septic patients and patients with SIRS had significantly higher baseline PCT values than patients with neither (median of 0.6, 0.36, and 0.28, respectively; p=.012 and .032 respectively) (Shomali *et al.,* 2012). Meidani *et al.* (2013) also analysed 64 cancer patients with FN and observed significantly higher PCT values in patients with sepsis than those without (mean PCT values 28.65 vs 2.48, p=.000).

The ROC (Receiver Operating Characteristic) curve for PCT (analysing its sensitivity and specificity) proved it to be accurate for predicting bacteremia and septic shock in 355 patients who developed FN: serum PCT ≥0.5 ng/mL was independently predictive of bacteremia (OR 3.96, 95%CI 1.51-10.4, p value of .005), whereas serum PCT ≥1.5 ng/mL was independently predictive of septic shock (OR 29.78, 95%CI 9.10-97.39, p value of <.001) (Ahn 2013).

Through 1,064 evaluated cancer patients, both febrile (575) and non-febrile (410), as well as 79 non-cancer individuals, the median baseline PCT values were higher in febrile cancer patients than in non-febrile ones (0.31 ng/mL vs 0.1 ng/mL, p<.0001). Furthermore, non-cancer patients had a significantly lower PCT median value than non-febrile cancer patients (0.029 vs 0.099 ng/mL, p<.0001). Among febrile patients, those with no microbiological infection had a significantly lower median PCT value than those with bacteremia or sepsis (0.31 ng/mL vs 0.49 ng/mL, p<.003) (Chaftari *et al.,* 2015).

On the other hand, some studies highlighted the lack of a precise correlation between high PCT values and infections in cancer patients with FN. Some studies (Carnino *et al.,* 2010, Diness *et al.,* 2014) showed that cancer patients had PCT levels which could not predict the development of an infectious episode. Considering 65 patients with solid tumors or leukemias at the time of leukocyte nadir, the authors noted that there was no difference in PCT values between patients who developed an infection than in those who did not (median of 0.7 ng/mL in both groups, p=0.85). *(*Carnino *et al.,* 2010). Moreover, in 41 cancer patients with clinical signs of infections, PCT was found to be a poor predictive marker for exclusion of bacterial infection in this setting, since the negative predictive value (NPV) of PCT within normal range was 0.56 (11 patients out of the 25 with an infection had normal PCT values, three of which had a bloodstream infection). They concluded that PCT values within normal range could not exclude an infection (Diness *et al.,* 2014).

Serial values

We found a lack of studies on the role of serial PCT measurements as an instrument of diagnosis of sepsis in cancer patients with FN. Jimeno *et al.* (2004) demonstrated that an increment of at least 50% from baseline PCT values was more common in patients with culture-documented infection than in patients with clinically-diagnosed infections or fever of unknown origin (p=0.032) (Jimeno *et al.,* 2004). If such use is confirmed in prospective studies, PCT might become a useful tool for the clinical management of FN.

Differences in different patient settings

The major controversies on the role of PCT as an early marker of sepsis in cancer patients with FN are due to the fact that several studies have shown that cancer patients, even in absence of septic episodes, tend to have higher PCT values than non-cancer patients. This increase in PCT values depends mainly on the type of cancer and the stage of the disease.

Leukemias seem to be associated with higher PCT values, compared with solid tumours (Carnino *et al.,* 2010). Among solid tumours, some, such as colon, thyroid, lymphoma, prostate, and sarcoma, seem to be related to a statistically higher PCT level (Carnino *et al.,* 2010, Chaftari *et al.,* 2015). Neuroendocrine differentiation *per se* seems to be associated with higher PCT levels (Patout *et al.,* 2014), but among lung cancers, non small cell lung cancers (NSCLCs) seem to be associated with higher levels as well (Scheinpflug *et al.,* 2015). Furthermore, when considering tumour stage, patients with advanced tumours seem to have higher PCT levels than patients with early-stage cancer (Shomali *et al.,* 2012, Chaftari *et al.,* 2015). Finally, one study (Carnino *et al.,* 2010) demonstrated that inpatients have higher PCT values than outpatients.

It was demonstrated that patients with haematological disorders had higher PCT values than patients with solid tumours (0.09 vs 0.05 ng/mL, p<.0015). PCT levels had

a direct correlation with the type of neoplasm (p=0.016), patients with acute leukemia having the highest concentrations. Furthermore, patients who were hospitalised had higher PCT values than outpatients (0.10 vs 0.05 ng/mL, p<.0013) (Carnino *et al.,* 2010). Another study confirmed that patients with haematological malignancies had higher median PCT values than those with solid tumours (0.23 ng/mL vs 0.156 ng/mL, p<.0001). Median PCT values were high in colon cancer (0.40 ng/mL), leukemia (0.26 ng/mL), thyroid cancer (0.231 ng/mL), lymphoma (0.165 ng/mL), prostate cancer (0.164 ng/mL), and sarcoma (0.147 ng/mL). Furthermore, non-cancer patients had lower median PCT values than patients with stage I-III cancer (0.029 ng/mL vs 0.127 ng/mL, p<.0001) or those with stage-IV disease (0.029 ng/mL vs 0.190 ng/mL, p<.0001). Among cancer patients, those with advanced-stage cancer had higher median PCT values than those with lower-stage disease (0.190 ng/mL vs 0.127 ng/mL, p=.004) (Chaftari *et al.,* 2015). Moreover, patients with advanced-stage cancer had significant higher baseline PCT values than patients with stage I to III cancer or in remission (0.47 vs 0.27 ng/mL), p=.017) (Shomali *et al.,* 2012).

Additional data showed that in patients with lung cancer a PCT serum level above 0.15 ng/mL was independently correlated to the presence of a neuroendocrine component in the tumour (HR=5.809, 95%CI 1.695-19.908, p=.0005). PCT values were higher in patients with small cell lung cancer (SCLC) than in patients with adenocarcinoma (ADC) (0.33 ng/mL vs 0.07 ng/mL, p<.001). Furthermore, PCT levels were significantly higher in patients with liver metastases (0.37 vs 0.09 ng/mL, p<.001). (Patout *et al.,* 2014). Non small cell lung cancer patients with elevated serum CRP levels were studied for infectious complications and then divided into two groups: infectious and not infectious. As far as prediction of infection is concerned, the areas under the ROC curve for PCT and CRP were 0.46 and 0.59, respectively, meaning that especially PCT cannot be considered a good discriminator between having or not having an infection in these patients (Sheinpflug *et al.,* 2015).

Clinical outcome

Some evidence was found on the role of PCT values in predicting the clinical outcome of these patients and the efficacy of the treatments in this patient setting. First of all, patients who experienced treatment failure demonstrated a greater proportion of positive values (considered as a baseline PCT value higher than 0.5 ng/mL) compared with patients who were treated successfully (70.0% vs 14.9%, p<.001) (Jimeno *et al.,* 2004). In addition, PCT levels at 4 to 7 days after fever onset were significantly lower than those at fever onset in those patients who experienced a response to antibiotic therapy (0.19 vs 0.52 ng/mL, p<.0001). On the other hand, PCT levels increased in those patients who experienced no response to antibiotics, but the difference was not significant (0.50 vs 0.43 ng/mL, p=.68) (Shomali *et al.,* 2012).

Cut-off

There is no consensus on the real cut-off that needs to be used to consider a PCT measurement positive or negative. Different cut-off levels have been used in the different studies to separate patients with a higher probability of developing infection from those with a lower risk; the cut-off used range from 0.17 ng/mL to 1.5 ng/mL, 0.5 ng/mL being the most common. Patients were also categorised according to a cut-off point of 0.5 ng/mL and it was observed that patients who had microbiologically documented infections (compared with patients with clinically diagnosed infections of fever of unknown origin) presented with a greater proportion of values higher than 0.5 ng/mL (66.7% vs 13.4%, p<0.001) (Jimeno *et al.,* 2004).

The ROC analysis for PCT concentrations was performed by applying the cut-off point of 0.5 ng/mL, PCT serum levels identified patients without infection with 100% specificity (with a 58% sensitivity); a cut-off point of 0.2 ng/mL could yield a higher sensitivity (79%), but a lower specificity (82.1%) (Schüttrumpf *et al.,* 2006). A similar cut-off point of 0.5 ng/mL was used in another study. Using this cut-off, the PCT test in this study had a sensitivity of 67%, specificity of 62%, PPV of 26%, and a NPV of 90% (Shomali *et al.,* 2012).

The first cut-off point of 0.5 ng/mL as an independent predictor of sepsis was subsequently confirmed. Furthermore, a cut-off point of 1.5 ng/mL was used to identify those patients at higher risk of septic shock (Ahn *et al.,* 2013).

ROC analysis was performed for the PCT test to differentiate febrile cancer patients with proven infection versus non-febrile cancer patients, obtaining an area under the curve of 0.80 (95%CI 0.76-0.83). The optimal cut-off value was 0.17 ng/mL, with a sensitivity of 81%, a specificity of 69%, a PPV of 54%, and a NPV of 89% (Chaftari *et al.,* 2015) (*Table 4*).

Correlation with Interleukin-6

IL-6 levels were measured in control patients and non-febrile cancer patients. A non-parametric correlation test was then performed, which showed a moderate positive correlation between IL-6 and PCT levels in these patients

Table 4 - *Cut-off, sensitivity and specificity of PCT in different studies.*

Study	*Cut-off*	*Sensitivity*	*Specificity*	*PPV*	*NPV*
Jimeno	0.5 ng/mL	66.7%	86.6%	-	-
Schüttrumpf	0.2 ng/mL 0.5 ng/mL	79.0% 58.0%	82.1% 100%	-	-
Shomali	0.5 ng/mL	67.0%	62.0%	26.0%	90.0%
Ahn	0.5 ng/mL (bacteremia) 1.5 ng/mL (septic shock)	71.0% 84.0%	82.0% 90.7%	30.0% 40.0%	97.0% 99.0%
Chaftari	0.17 ng/mL	81.0%	69.0%	54.0%	89.0%

(CC=.41, p<.0001). Furthermore, the median IL6 level in the control group was significantly lower than in patients with low-stage or advanced cancer (0 vs 7.376 vs 9.635 pg/mL, p<.0001). However there was no significant difference between patients with low-stage cancer and those with advanced cancer (Chaftari *et al.,* 2015).

Combination of PCT with risk assessment scales

Several scales are available in everyday clinical practice to assess the risk of infective episodes in cancer patients who develop FN. It would be interesting to investigate if adding PCT values to these scales might be useful to increase the accuracy of these tools in predicting such risk.

The combined risk assessment, obtained by taking into consideration both PCT values and Talcott risk-assessment scale, increased sensitivity for the detection of bacteremia from 73.3% to 93.3% (p=0.31) and the NPV from 93.1% to 98.0% (p=0.37). Similar values were obtained, using MASCC scale and PCT values for the combined risk assessment (increased sensitivity for the detection of bacteremia from 60.0% to 86.7%, with p=0.19, and increased of NPV from 92.0% to 96.8%, with p=0.29) (Jimeno *et al.,* 2004). Furthermore, adding PCT to MASCC score could be useful, especially in those patients considered at low risk: in fact, of the 19 low-risk patients who developed bacteremia, 12 (63%) had PCT ≥0.5 ng/mL; of the 8 low-risk patients who developed septic shock, 7 (87.5%) had PCT ≥1.5 ng/mL (Ahn *et al.,* 2013).

A recent study examined the use of PCT (as well as other plasma biomarkers) together with the Glasgow Prognostic Scale (GPS) in cancer patients who develop some cancer-related urgency, such as fever and infectious complications, but also cancer progression or local cancer complications, and worsening of general conditions (Rast *et al.,* 2015). GPS is commonly used to assess the long-term mortality of cancer patients, but it is being studied in order to understand whether it can be used to assess short-term prognosis during cancer-related urgencies.

The study highlighted that GPS is associated with 30 day mortality, and PCT (as well as other biomarkers, that include 25(OH)-vitamin D, urea, and corrected calcium) had the best prognostic performance among serum biomarkers (OR 1.6, 95% CI 1.3-1.9; AUC 0.69, 95% CI 0.63-0.76). When combined with GPS, it improved its accuracy (AUC 0.74, 95% CI 0.68-0.80, p<0.001). These data might suggest improving PCT uses during emergencies in order to predict the outcome of cancer patients developing related acute conditions. However, such hypothesis should be further investigated with proper randomised clinical trials.

Correlation with short-term mortality

Recent evidence suggests that PCT serum levels might be of use in predicting short-term mortality in cancer patients who develop emergencies and infectious severe complications. Rast *et al.* (2015) evaluated the use of PCT in patients who develop cancer-related emergencies. PCT showed a high prognostic performance (OR 1.6 95% CI 1.3-1.9) when used as an early biomarker of short-term mortality. In a further study (Sedef *et al.,* 2015), PCT was considered a mortality biomarker in patients developing infectious complications and its possible use was highlighted for an early understanding of the severity of the infectious episode to help in the decision-making process and possibly reduce mortality.

DISCUSSION

Considering the general population (regardless of oncological comorbidities), PCT serum levels have been widely studied and it is generally accepted that PCT can be clinically useful for the early identification of patients who are developing infectious episodes, especially sepsis. However, are some issues still need to be solved and PCT cannot be considered an ideal sepsis biomarker at the moment.

Despite this, in the last few years a major interest has arisen in understanding whether PCT serum values could be useful in oncological patients as well.

In fact, an early diagnosis of infectious complications in cancer patients, especially in those with neutropenia and FN, might change these patients' natural history, since infections still represent a major cause of mortality and one of the most common causes of reductions and delays in cancer therapy.

Most of the studies we considered in our review found PCT serum levels were significantly higher in cancer patients with an ongoing infectious episodes. Some studies suggest that PCT values are higher during major infectious complications, such as bloodstream infections, sepsis, and septic shock, when compared with patients with minor infectious episodes (such as localized infections). Such results might encourage the use of PCT when there is a clinical suspicion of major infectious complications, whereas it might be discouraged in case of localized infections, such as skin infections.

Some evidence recommends the use of serial PCT evaluations in clinical practice. In fact, this might increase sensitivity and specificity in the diagnostics of infections and sepsis: an increase in PCT levels over time is suggestive of the development of an infectious episode. Such clinical behaviour could also be of use in evaluating responses to antibiotic therapy: some studies suggest that a decrease in PCT levels is indicative of a good response to treatment and, consequently, a better outcome. PCT accuracy could also be increased, if used together with other risk assessment scales, such as MASCC score or Talcott scale. Some studies highlight the possibility of using PCT in emergency situations (among which, infectious complications) in order to predict the short-term mortality risk of cancer patients.

The studies we analysed also highlight several issues in the use of PCT serum levels in the diagnostics of infections and sepsis. The first thing to consider is that the literature-based evidence we have is taken from different studies considering different settings of patients (that is, patients with haematological malignancies versus solid tumours, patients with early-stage versus advanced cancers).

That makes it harder to obtain solid evidence that can be applied to all cancer patients, since it is logical to think that different types and stages of cancer might affect the patients' immunological and inflammatory status and hence PCT values.

Secondly, several studies did not specify the laboratory method used to determine PCT levels. There are several technical methods on the market and there is no internationally validated technique. This makes it difficult to compare PCT determinations done in the different centres and might be confusing when patients are evaluated in different centres during their clinical history.

Thirdly, studies considered different cut-offs to divide pos-

itive from negative results. Using a lower cut-off might be useful to increase sensitivity, but might affect negatively its specificity. On the other hand, a higher cut-off could increase its specificity, but decrease its sensitivity. Furthermore, it is important to define a standard cut-off if PCT is to be used routinely in everyday clinical practice, in order to make it possible to compare different results obtained in different centres or at different times. Finally, it is important to consider the cost of the determination of PCT values.

Compared to other commonly used inflammatory markers (such as CRP), PCT is more expensive to determine, and if we consider the potential use of serial determinations, this aspect is to be carefully evaluated.

Some of the issues found in the studies could be overcome. PCT could, in fact, be used in combination with other laboratory tests or clinical instruments. As far as laboratory tests are concerned, major interest is given to new biomarkers, such as CD64 and IL-6. Compared with a single test, the use of a panel of tests might increase the diagnostic accuracy of sepsis and infectious episodes, even if this could also increase the costs of the diagnosis. Such behaviour could then be applied to patients with a higher suspicion of major infectious disease. On the other hand, the use of PCT values together with risk assessment scales, such as MASCC or Talcott, could increase diagnostic specificity and sensibility with no further costs and minimal clinical effort.

Some evidence suggests that PCT values change during the natural history of infectious complications, increasing from the pre-clinical to the clinical phase of infections and lowering once proper antimicrobial treatment is begun and there is a good response to therapy. It is then consistent to think that measuring PCT serum levels periodically from the time of diagnosis until treatment and resolution of the episode might be useful to predict response to specific anti-microbial treatment and to modify the therapy in those patients who do not respond. However, such hypothesis needs to be demonstrated, since the possible interference of anticancer drugs on PCT values must be excluded.

Analysing the overall results of the studies we considered, it is credible to think that PCT use in everyday clinical practice, preferably in combination with other clinical or laboratory instruments, might be of help in finding and detecting early infectious complications in cancer patients, but further *ad hoc* studies are needed to confirm this hypothesis.

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