Original paper

Monitoring inflammation in patients diagnosed with non-small cell lung and colorectal cancer using blood levels of C-reactive protein, procalcitonin, and plasma gelsolin

Monitorowanie stanu zapalnego u pacjentów ze zdiagnozowanym rakiem niedrobnokomórkowym płuc i rakiem jelita grubego z wykorzystaniem oceny poziomu białka C-reaktywnego, prokalcytoniny i gelsoliny osoczowej we krwi

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Key words: plasma gelsolin, C-reactive protein, procalcitonin, non-small cell lung cancer, colorectal cancer.

Słowa kluczowe: gelsolina osoczowa, białko C-reaktywne, prokalcytonina, niedrobnokomórkowy rak płuca, rak jelita grubego.

Abstract

Introduction: Plasma gelsolin (pGSN) was recently introduced as a new predictor of systemic inflammation outcomes, especially in critically ill patients. This study aimed to describe the potential interplay between C-reactive protein (CRP), procalcitonin (PCT), and pGSN concentrations in blood collected from patients diagnosed with colon and lung cancer and to assess their diagnostic potential when a combined evaluation of those 3 markers was performed.
Aim of the research: We hypothesized that a correlation between increased blood levels of CRP and PCT and a decreased level of plasma gelsolin might help identify cancer-associated inflammatory responses and a higher risk of poor clinical outcomes.
Material and methods: Blood samples collected from 159 subjects were subjected to the biochemical analysis of CRP and PCT, in addition to the assessment of pGSN levels using Western blotting.
Results: Our results confirmed a significant increase in CRP and PCT concentrations in collected blood samples, while pGSN concentrations decreased. Because the values of the blood CRP, PCT, and pGSN concentration did not show a strong correlation within the tested groups, it might be assumed that the molecular and cell signalling background leading to changes in those markers differs.
Conclusions: A better understanding of the clinical value of the simultaneous evaluation of CRP, PCT, and pGSN levels in patients suffering from rectal and lung cancer might help us identify those with inflammatory responses leading to poor clinical outcomes.

Streszczenie

Wprowadzenie: Gelsolina osoczowa (pGSN) od niedawna traktowana jest jako nowy predyktor ogólnoustrojowych następstw procesów zapalnych, zwłaszcza u pacjentów w ciężkim stanie klinicznym. Nasze prace były ukierunkowane na zbadanie potencjalnej zależności między stężeniem białka C-reaktywnego (CRP), prokalcytoniny (PCT) i pGSN we krwi pobranej od pacjentów z rakiem jelita grubego i płuca oraz ocena ich potencjału diagnostycznego, gdy prowadzono łączną ocenę tych trzech markerów.
Cel pracy: Weryfikacja hipotezy, że istnieje korelacja pomiędzy podwyższonym stężeniem CRP i PCT we krwi a zmniejszonym stężeniem gelsoliny osoczowej, co może pomóc w identyfikacji systemowej odpowiedzi zapalnej zależnej od procesu nowotworowego u tych pacjentów i związanego z tym gorszego rokowania u tych chorych.
Materiał i metody: Próbki krwi pobrano od 159 osób, poddano je analizie biochemicznej; oznaczono CRP i PCT oraz poziom pGSN za pomocą metody Western blot.

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Wyniki: Badania wykazały istotny wzrost stężeń CRP i PCT w pobranych próbkach krwi, natomiast stężenie pGSN było zmniejszone. Ponieważ wartości stężeń CRP, PCT i pGSN we krwi nie wykazywały silnej korelacji w obrębie badanych grup, można przypuszczać, że za zmiany te odpowiadają odmienne mechanizmy molekularne.
Wnioski: Lepsze zrozumienie wartości klinicznej jednoczesnej oceny stężeń CRP, PCT i pGSN u pacjentów cierpiących na raka jelita grubego i raka płuc może pomóc w identyfikacji chorych z ogólnoustrojową reakcją zapalną, niosącą za sobą gorsze rokowanie.

Introduction

An important relationship between inflammation, the so-called "mother of disease", and cancer has been postulated in a significant number of studies [1, 2]. Inflammation is a critical component of tumour progression and is responsible for excess morbidity and mortality in cancer patients. Recognizing the inflammatory status of patients suffering from cancer is crucial, but those subjects often present minimal signs, usually due to their immunocompromised status. The biochemical assessment of inflammation is usually based on defined blood markers such as C-reactive protein (CRP) and/or procalcitonin (PCT) concentrations. However, accurate interpretation of their levels in blood collected from oncological patients can be challenging. It has been demonstrated that local and systemic inflammation are an integral part of oncological diseases, including lymphoma, hepatocellular carcinoma, mesothelioma, and lung and colon cancers [3, 4]. Moreover, the immune system stimulation associated with tumour growth leads to permanent inflammation that promotes cancer cell proliferation and dissemination [5]. On the other hand, patients with cancer frequently require the management of systemic and localized infections. In those clinical situations, the inflammatory response is mostly driven by the progression of infections, and its risk is several times higher in oncological patients than in non-malignant patients. Overall, systemic inflammation in response to infection is mostly responsible for the excess morbidity and premature mortality in cancer patients [6, 7]. It has been suggested that, in oncologic subjects, skin and mucosal barrier disruption are the major predisposal factors leading to the development of inflammation due to bacterial translocation (BT) to extraluminal sites [8]. However, this group of patients manifests minimal signs even when serious inflammation takes place and progresses. Therefore, rapid diagnosis and subsequent treatment are crucial to survival. Thus, it is important to detect an inflammatory status and associated infections as soon as possible. One way to do this is by monitoring inflammatory blood markers such as CRP and PCT [9]. Besides CRP and PCT, other markers such as the erythrocyte sedimentation rate, amyloid A, a1-acid glycoprotein, ceruloplasmin, hepcidin, haptoglobin, and cytokines are also in use. CRP is produced by hepatocytes and is a member of the acute phase reactant proteins family. The CRP level in blood is monitored to detect and assess conditions that cause inflammation, such as infections, sepsis, autoimmune disorders, and various cancers. PCT was first introduced to the biomedical literature in 1975. It is a 116-amino acid prohormone of calcitonin, produced mainly by C-cells of the thyroid gland [10, 11]. It is rarely detected in healthy subjects (< 0.1 ng/ml); however, in case of infection, procalcitonin is synthesized in almost all tissues and organs throughout the body. During inflammation, especially when caused by bacterial sepsis, its production is induced by several stimuli, including bacterial endotoxins or pro-inflammatory cytokines [12]. However, the appropriate interpretation of the PCT increase in cancer patients might be difficult because many factors, including metastasis and the endocrine function of the tumour, can significantly affect its values. Some authors have postulated that the elevated PCT in oncological patients with the generalized disease cannot be attributed to infection but may be regarded as a marker for the oncological progression [13]. However, other studies of PCT levels in aseptic patients with solid tumours did not mention any significant changes [14]. Extracellular plasma gelsolin (pGSN) is an actin-binding protein that is an important part of the blood F-actin scavenging system; it eliminates potentially harmful actin molecules released into the blood from injured tissues [15]. Plasma GSN is not considered an acute phase reactant; however, it falls significantly in severe sepsis, and its loss impairs actin clearance and, in that manner, promotes inflammatory cytokine generation. Its low levels are correlated with disease severity and bad clinical outcomes [16–18]. The functions of extracellular and cytoplasmic (intracellular) gelsolin differ significantly. Cytoplasmic gelsolin is mostly associated with cell cytoskeleton remodeling. It was proven that cytoplasmic gelsolin expression was modified in several human cancers; however, the potential implication of this protein in carcinogenesis is not fully understood [19]. Because there are data showing that gelsolin production is markedly reduced in colon cancer cell lines, it has been postulated that it could play a key role as a tumour suppressor in malignancy [20]. Overall, it is not known if the production of gelsolin by cancer cells interferes with its blood concentration, which is supplied by pGSN production in muscle cells. Interestingly, the functions of intracellular gelsolin are controlled by Ca^{2+} and membrane phosphatidylinositol (PPI), predominantly $PI(4,5)P_2$, and the gelsolin domains binding PPI can also preferentially interact with other bioactive lipids

such as lysophosphatidic acid (LPA), sphingosine-1 phosphate (S1P), platelet-activating factor (PAF), and bacterial wall products including LPS (lipopolysaccharide) and lipoteichoic acid (LTA). Such interactions in the blood might result in the formation of molecular complexes that are taken up by endothelial cells and tissue macrophages – a process that accounts for gelsolin depletion [21–23]. Additionally, the interaction of pGSN with bioactive lipids might interfere with the inflammatory response, especially when induced by bacterial wall products, because the LPS/LTA interaction with TLRs (toll-like receptors) was found to be prevented by recombinant human plasma gelsolin [24]. Taking into account the complex interaction of pGSN with actin released from injured cells and bioactive lipids that might be generated during the inflammatory response, we propose investigating the use of blood levels of plasma gelsolin as a marker of the inflammatory response in patients diagnosed with the most frequently occurring lung and colon cancers. We assume that the plasma gelsolin level might be especially helpful for monitoring the inflammatory response in the above conditions because cancer growth within the walls of the bronchi or the gastrointestinal lumen (which are colonized by bacteria) might result in a nonspecific increase in CRP and PCT as a consequence of natural microbiota translocation. Overall, pGSN assessment might improve the identification of subjects at higher risk of poor outcomes because a pGSN decrease was found to correlate with the occurrence of multiple organ dysfunction syndrome (MODS) [25]. On the other hand, the administration of recombinant plasma gelsolin was proposed as a potential intervention to prevent the negative consequences associated with hypogelsolinemia [26].

Aim of the research

We believe that an improved understanding of the role of inflammation in cancer and the potential functions of pGSN in these conditions may lead to new uses of this protein in diagnosis and treatment.

Material and methods

Subjects

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Jan Kochanowski University of Kielce, Poland (approval no. 13/2015). Patients' written consent was obtained to submit the study. The enrolment in the study took place between March 2017 and March 2022 in the Holy Cross Oncology Centre of Kielce. In this study we selected patients with the most common cancers in our region. Patients were recruited immediately after the diagnosis of malignant neoplasm; selected patients were at different stages of the disease.

Table 1. Demographic characteristics of patients with colorectal cancer: number of patients, age, sex, and clinical stage

Variable	Value
Patients diagnosed with colorectal cancer, *n*:	58
Age [years]:	
Mean ± SD	66 ±10.7
Range	52–80
Sex, *n* (%):	
Male	33 (57)
Female	25 (43)
Colorectal cancer localization, *n* (%):	
Rectum	26 (45)
Colon	32 (55)
Control, *n*:	30
Age [years]:	
Mean ± SD	42 ±17.3
Range	23–68
Sex, *n* (%):	
Male	13 (43)
Female	17 (57)

Clinical advancement: I – 10%, II – 13.3%, III – 53.4%, IV – 23.3%.

Fifty-eight patients with colorectal cancer (32 with colon cancer and 26 with rectal cancer), 71 patients with non-small cell lung cancer (21 with not otherwise specified lung cancer (NOS), 23 with squamous cell lung cancer (SCC), and 27 with adenocarcinoma (AC). The inclusion criteria were as follows: 1) over 18 years old, 2) the absence of any chronic inflammatory disorders in the past (based on hospital records and interviews), 3) a confirmed diagnosis of cancer based on histopathological examination, and 4) nonfebrile patients. The exclusion criteria were as follows: 1) a lack of written consent, and 2) the onset of symptoms of any acute inflammation 7 days before the examination. All the patients (Tables 1 and 2) received standard oncological treatment appropriate to the stage of the disease. The control group comprised healthy volunteers, similar to the studied group with respect to sex and age. They were professionally active, without serious chronic diseases, and were admitted to work by an occupational medicine doctor.

Evaluation of CRP and PCT concentration

CRP concentration was determined by an immunoturbidimetric assay of the quantitative determination on a Cobas c501 analyser (Roche Diagnostics GmbH, Mannheim, Germany). PCT measurement was performed using an electrochemiluminescence

Table 2. Demographic characteristics of patients with lung cancer (NSCLC): number of patients, age, sex, and clinical stage

Variable	Value
Patients diagnosed with lung cancer, *n* :	71
Age [years]:	
Mean ± SD	69 ±7
Range	59–81
Sex, *n* (%):	
Male	50 (70)
Female	21 (30)
Cancer type:	
NOS	21 (30)
SCC	23 (32)
Adenocarcinoma	27 (38)
Control, *n*:	30
Age [years]:	
Mean ± SD	42 ±17.3
Range	23–68
Sex, *n* (%):	
Male	13 (43)
Female	17 (57)

Clinical advancement: IB – 2%, IIA – 2%, IIB – 8%, IIIA – 8%, IIIB – 25%, IIIC – 4%, IV – 49%.

assay on a Cobas e411 immunoassay analyser (Roche Diagnostics GmbH, Mannheim, Germany).

Western blotting quantification

Plasma samples were diluted 1 : 100 with PBS and then denatured in sample buffer for 10 min at 95°C and subjected to electrophoresis using 10% sodium dodecyl sulphate-polyacrylamide electrophoresis (SDS-PAGE). The samples placed in each gel were accompanied by a recombinant human plasma gelsolin (pGSN) standard with a concentration range comparable to the gelsolin concentration in the samples. After SDS-PAGE separation, proteins were electrophoretically transferred onto polyvinylidene fluoride membranes (Amersham Biosciences, Little Chalfont, UK). Next, the membranes were submerged in methanol, then blocked for 1 h in 5% nonfat dry milk in TBS-T (150 mM NaCl, 50 mM Tris Base, 0.05% Tween 20, pH = 7.4). The transferred proteins were incubated on a rocking platform at 4°C in the dark overnight with a monoclonal anti-GSN primary antibody produced in mice (Sigma, St. Louis, MO, USA), diluted at 1 : 10,000 with TBS-T. After incubation, the primary antibody was decantated, and membranes were flushed 3 times for 15 min with TBS-T, with constant shaking. The buffer was removed, and an IRDye 800CW goat polyclonal Anti-Mouse IgG secondary antibody at 1 : 20,000 dilution in TBS-T was added for 1 h. The secondary antibody was removed, and the membranes were flushed, as previously mentioned. The membrane was rinsed with TBS to remove the remaining Tween 20 (150 mM NaCl, 50 mM Tris Base, pH = 7.4). The Western blots were quantified fluorometrically using the Odyssey Imaging System (LI-COR Biosciences, Lincoln, NE, USA). The standard curve for the determination of pGSN concentration was prepared using gelsolin concentrations of 7.5, 10, and 15 ng/µl. The intensity of each band on the Western blot, excluding the background signal, was plotted against the known amount of gelsolin and fitted to a straight line ($R^2 \geq 0.9$); the graph was used as a standard curve to evaluate unknown gelsolin levels in simultaneously assayed patient samples [27].

Statistical analysis

Quantitative data are expressed as mean ± SD. Statistical analyses were evaluated using the unpaired Student's *t*-test, with $p < 0.05$ considered statistically significant. Pearson's correlation test was used to compare values of CRP, PCT, and plasma gelsolin levels among patients.

Results

CRP, procalcitonin, and plasma gelsolin concentrations in blood samples collected from patients diagnosed with lung cancer

We noted a significant increase in CRP levels in all the groups of patients diagnosed with non-small cell lung cancer (22.45 ±25.74 mg/l; range: 0.7–99.24) compared to controls (2.64 ±1.22 mg/l; range: 0.65–4.9) (Figure 1 A). We observed a significant reduction in the pGSN concentration in the blood of patients with NOS (113.59 ±54.12 µg/ml), SCC (123.99 ±59.66 µg/ml) and adenocarcinoma (115.03 ±54.43 µg/ml) compared to the control group (172.83 ±51.31 µg/ml) (Figure 1 C). In the whole studied group of lung cancer patients, we noticed an increase in the PCT concentration (0.077 ±0.095 ng/ml; range: 0–0.47) compared to controls (< 0.02 ng/ml; range: 0–0.019) (Figure 1 B).

Correlation of pGSN concentration with diagnostic markers of inflammation in patients diagnosed with lung cancer

We did not find any statistically significant correlation between pGSN and CRP and PCT levels in lung cancer patients (Figures 2 A, B, D, E, G, H, J, K). As shown in Figure 2 A, we observed a weak negative correlation (not statistically significant) between pGSN and CRP in NOS patients. A weak positive cor-

relation (not statistically significant) was observed between PCT and CRP levels in NOS, SCC, and adenocarcinoma patients (Figures 2 C, F, I, L).

CRP, procalcitonin, and plasma gelsolin concentrations in blood samples collected from patients diagnosed with colorectal cancer

As shown in Figure 3 A, we observed a significant increase in CRP levels in all colon cancer groups. Similarly to the lung cancer group, we noted a significant increase in PCT concentration (0.06 ±0.05 ng/ml; range: 0–0.27) compared to the controls (< 0.019 ng/ml) (Figure 3 B). A reduction in pGSN was observed in the blood of all patients with colorectal cancer; the concentration of gelsolin measured in the plasma obtained from patients diagnosed with rectal cancer was 90.13 ±40.39 μg/ml and with colon cancer it was 97.19 ±47.91 μg/ml (Figure 3 C). Statistical significance was also reached when we comparing pGSN obtained from all colorectal patients (94.03 ±44.45 μg/ml) with the control group (172.83 ±51.31 μg/ml).

Correlations of pGSN concentration with diagnostic markers of inflammation in patients diagnosed with colorectal cancer

We did not find any statistically significant correlation between the concentrations of pGSN and CRP and pGSN and PCT in patients diagnosed with colorectal cancer (Figures 4 A, B, D, E, G, H). We observed a weak negative correlation (not statistically significant) between pGSN and CRP in all colorectal patients. There was no correlation between PCT and CRP in these patients (Figures 4 C, F, I).

Discussion

The inflammation associated with infections in cancer patients often occurs with minimal signs and symptoms but can progress rapidly; therefore, early detection and appropriate treatment are crucial. The risk of developing an infection is relatively high for oncology patients due to the haematological toxicity of chemo- and radiotherapy, leading to neutropaenia. It is also believed that skin and mucosal barrier disruption, leading to bacterial translocation (BT), acts as a predisposing factor crucial to systemic inflammation and sepsis. BT occurs when live microorganisms or their products pass from intraluminal sites outside [28]; this may be observed during the dysfunction of cell-mediated immunity, the obstruction of the bronchial tree, or any parts of the gastrointestinal tract during cancer growth, or some diagnostic and therapeutic procedures [9]. In some cases, BT might lead to sepsis, the systemic inflammatory response to infection, if not diagnosed and appropriately treated; sepsis is frequently responsible for severe clinical manifestations and death [29].

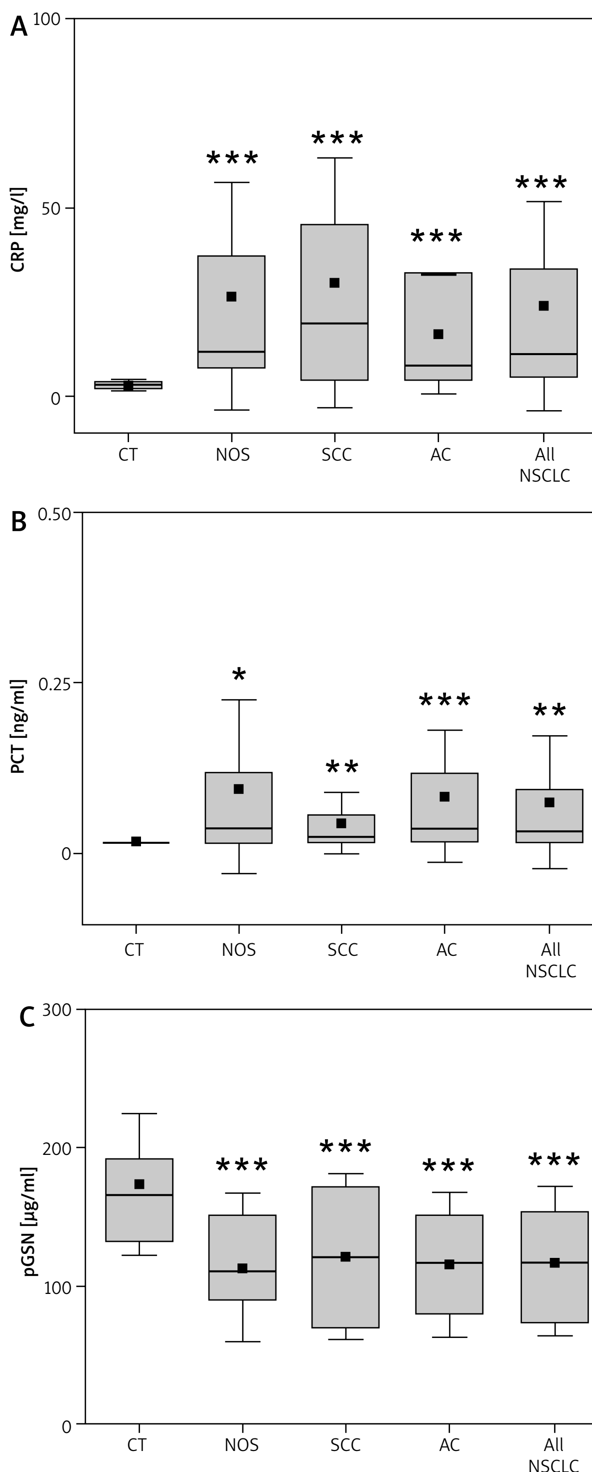

Figure 1. Concentrations of C-reactive protein (**A**), procalcitonin (**B**), and plasma gelsolin (**C**) in plasma obtained from patients diagnosed with different subtypes of non-small-cell lung cancer. Not otherwise classified NSCLC (*n* = 21), squamous cell lung cancer (*n* = 23), lung adenocarcinoma (*n* = 27), and combined values from all tested lung carcinomas (*n* = 71), compared to control samples (*n* = 30). Data are presented as mean ± SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ by unpaired Student's *t*-test

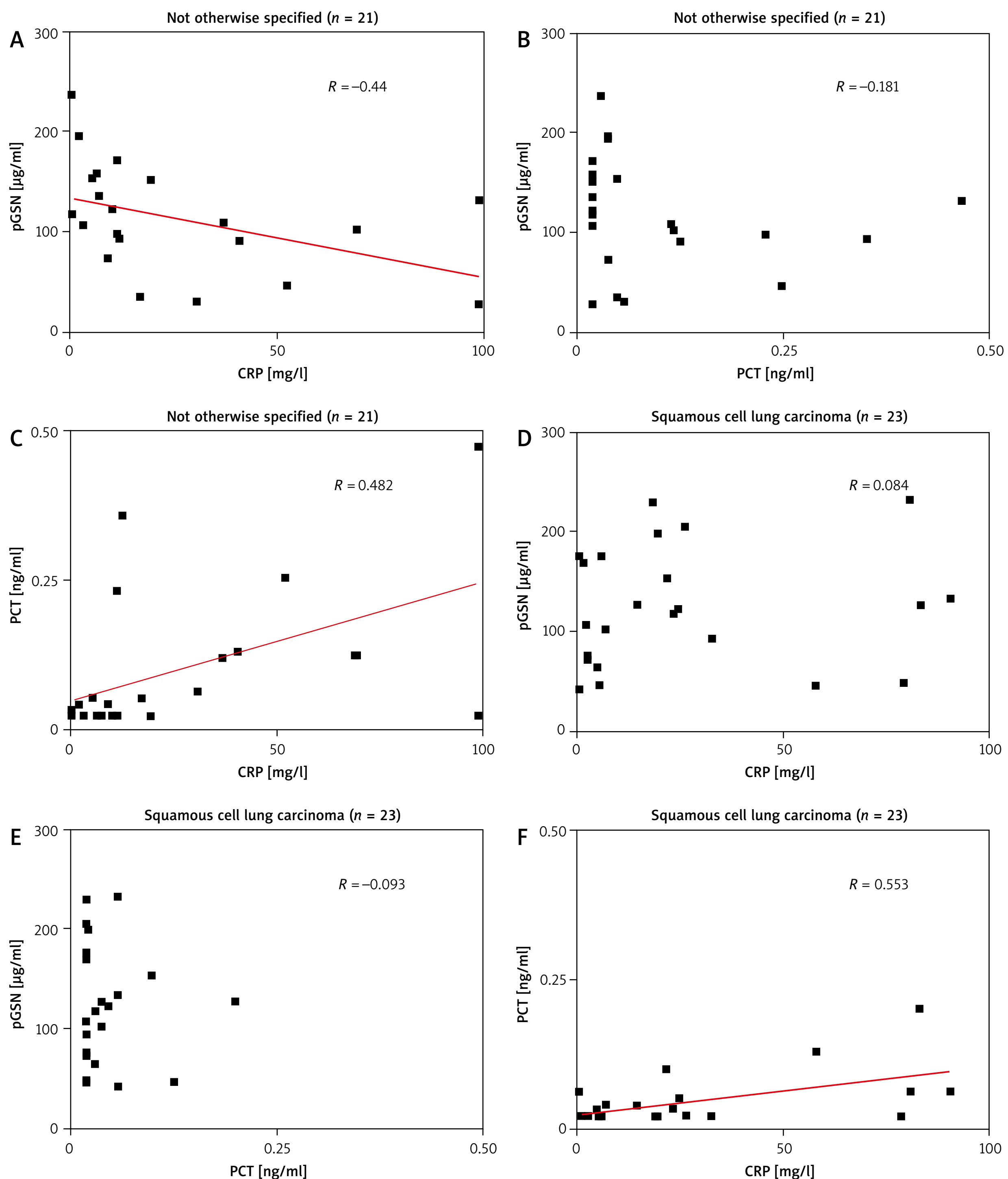

Figure 2. Assessment of potential correlation between concentrations of plasma gelsolin (pGSN) and C-reactive protein (CRP) (**A, D, G, J**), gelsolin and procalcitonin (PCT) (**B, E, H, K**), PCT and CRP (**C, F, I, L**) in plasma obtained from patients diagnosed with lung cancer. The red line indicates Pearson's $R < -0.2$ or > 0.2

Unfortunately, its diagnosis is difficult among cancer patients because classic symptoms of inflammation such as fever, leukocytosis, and an elevated CRP concentration are common in this group, even in the absence of infection. Even PCT, produced by macrophages or neuroendocrine cells in response to endotoxins and widely recognized as a specific marker of sepsis, might be influenced by many factors, especially in advanced tumours. It has been documented that many advanced cancers with metastasis could

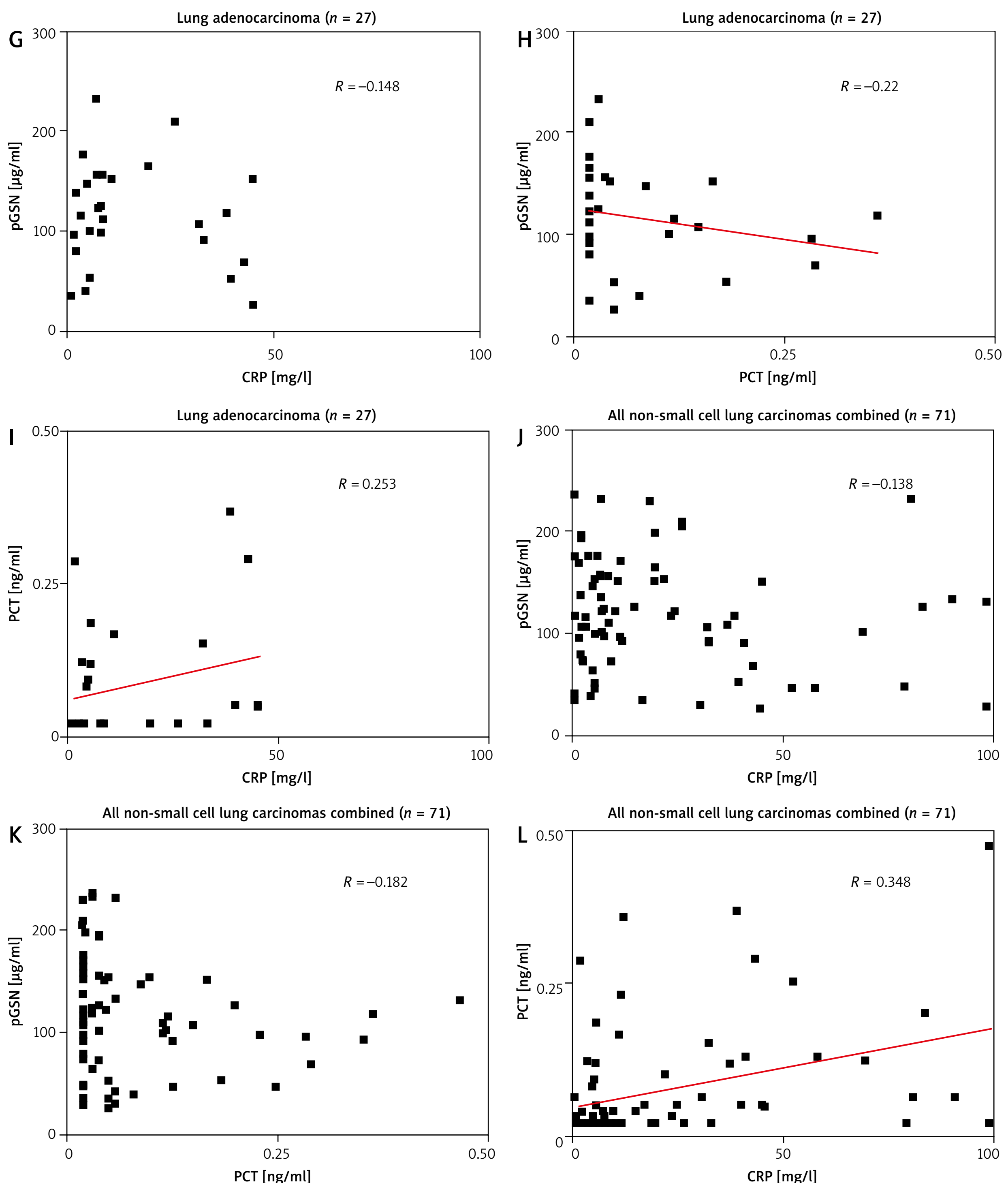

Figure 2. Cont.

increase the PCT level via tumour necrosis factor and interleukins pathways [30], or the increase could be related to mucosal barrier disruption and not sepsis development. In our study, we observed a significant increase in CRP and PCT concentrations in both colon and lung cancer patients without sepsis. Moreover, we found a slight positive correlation between PCT and CRP in the lung cancer group, while no correlation was noticed in the group with colorectal cancer.

On the other hand, PCT levels did not change significantly when measured in patients with advanced carcinoma [14]. This suggests that factors other than CRP and PCT might be of use in diagnosing inflammation and its complications in cancer pa-

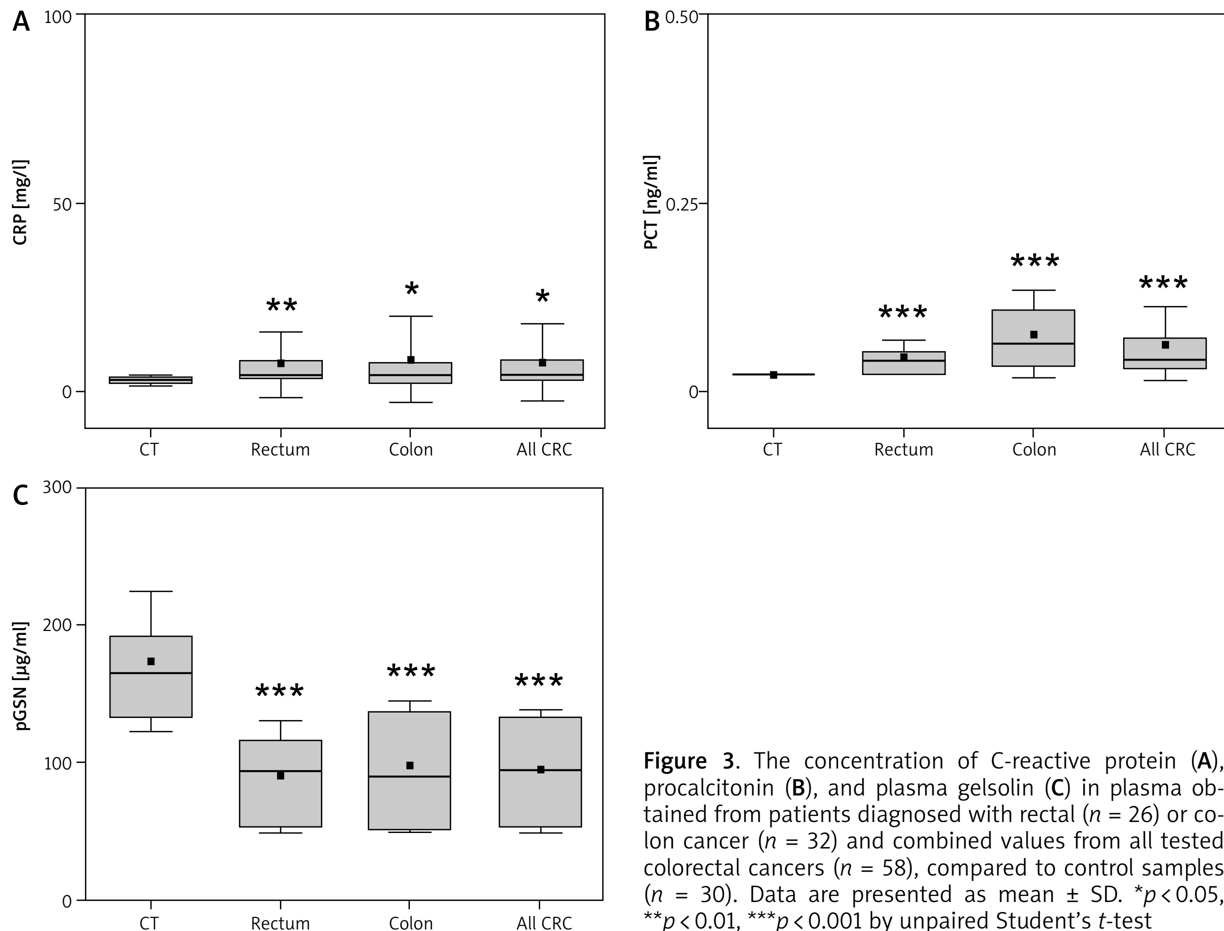

Figure 3. The concentration of C-reactive protein (**A**), procalcitonin (**B**), and plasma gelsolin (**C**) in plasma obtained from patients diagnosed with rectal (n = 26) or colon cancer (n = 32) and combined values from all tested colorectal cancers (n = 58), compared to control samples (n = 30). Data are presented as mean ± SD. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ by unpaired Student's t-test

tients. Therefore, better diagnostic tools are needed to identify those cancer patients developing infections during the progression of oncological disease. Considering the predictive value of plasma gelsolin depletion, based on our data, we cannot conclude that the assessment of plasma gelsolin concentration is potentially helpful for identifying patients at higher risk of MODS because its low concentration did not strongly correlate with a high concentration of CRP or PCT. However, the evaluation of plasma gelsolin might be of value in patients because the inflammatory process leading to hypogelsolinemia cannot be screened for by CRP or PCT assessment. The importance of plasma gelsolin monitoring was justified by our previous study, which indicated that mortality was lower in patients with leukaemia suffering from sepsis when a high PCT concentration was recorded, and patients maintained their pGSN level [31].

In addition, we noted an increase in PCT concentration (though to different extents) in all groups of cancer patients not suffering from sepsis. Therefore, we postulate that damage of the mucosal barrier, caused by cancer growing into the lumen of the airways or colon, might be a cause of bacteraemia, which is responsible for PCT elevation. Therefore, such a possibility should be considered when interpreting the PCT value in lung or colon cancer patients. It is worth underlining that bacterial presence in the blood might be a factor causing plasma gelsolin depletion as a consequence of the possible direct interaction of bacterial products (such as LPS or LTA) with pGSN. Metabolites released by bacterial cells aggregate with pGSN in complexes that are likely eliminated by the endocytosis pathway, with the involvement of endothelial and liver cells. The potential benefit of adding pGSN as an additional marker to CRP and PCT to monitor inflammation in lung and colon cancer patients is justified by the possibility of a nonspecific increase in PCT in these patients and by data obtained in previous studies indicating that the pGSN concentration is particularly diminished during tissue injury, the development of secondary organ damage, and critical care complications such as burn-induced pulmonary microvascular dysfunction [32]. Interestingly, other studies showed that the decrease in pGSN concentration in such patients is inversely correlated with illness severity, as well as with overall in-hospital mortality [33, 34]. Therefore,

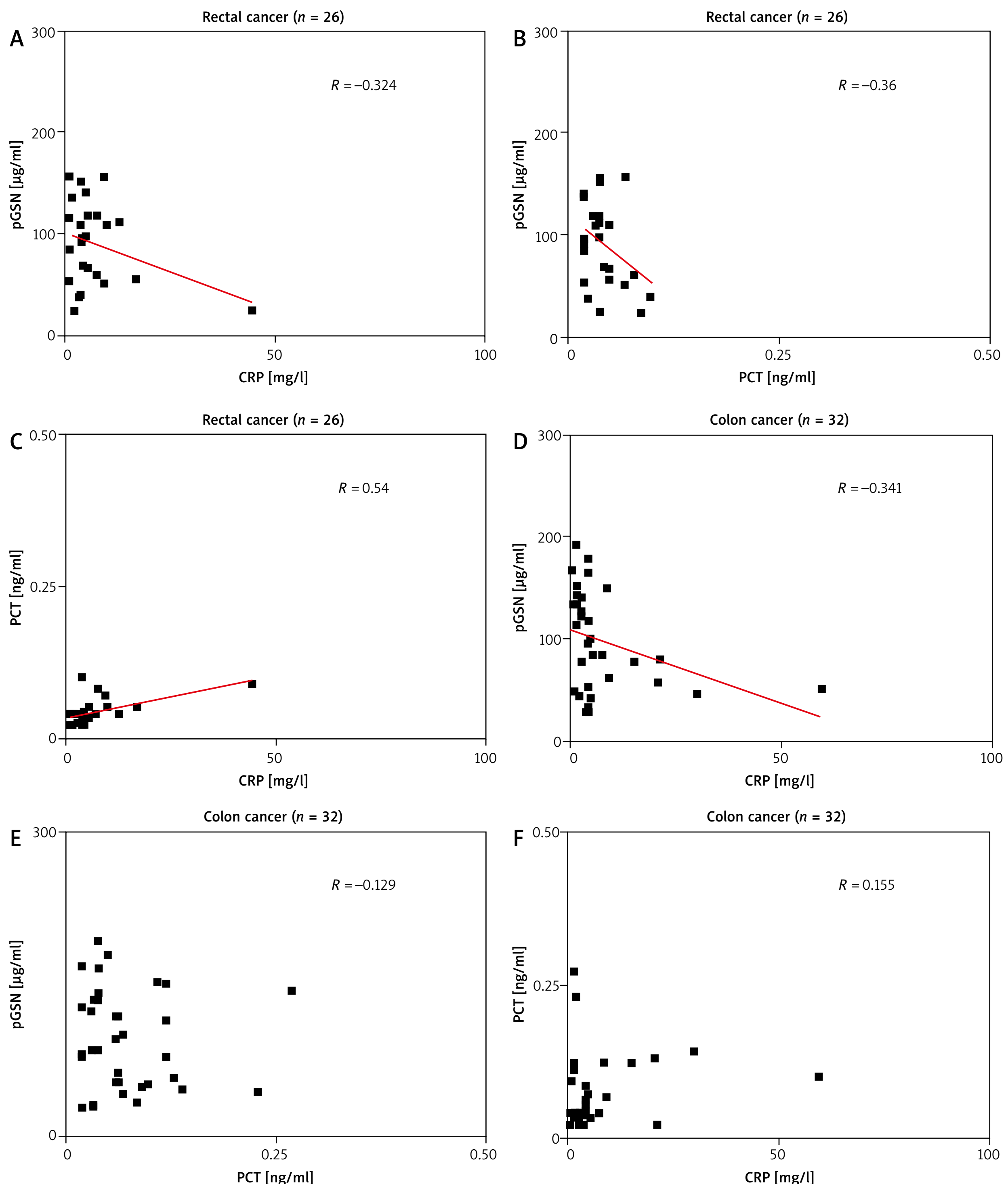

Figure 4. Assessment of potential correlation between concentrations of plasma gelsolin (pGSN) and C-reactive protein (CRP) (**A, D, G**), gelsolin and procalcitonin (PCT) (**B, E, H**), PCT and CRP (**C, F, I**) in plasma obtained from patients diagnosed with colorectal cancer. The red line indicates Pearson's $R < -0.2$ or > 0.2

pGSN depletion can be recognized not only as a valuable predictor of inflammation and tissue injury, but also as an indicator of poor prognosis in most clinical settings when dealing with seriously ill patients.

In our study, we have shown a significant decrease in the concentration of pGSN in the blood of patients with colon cancer or all studied lung cancers (NOS, SCC, and AC). All studied groups had elevated PCT

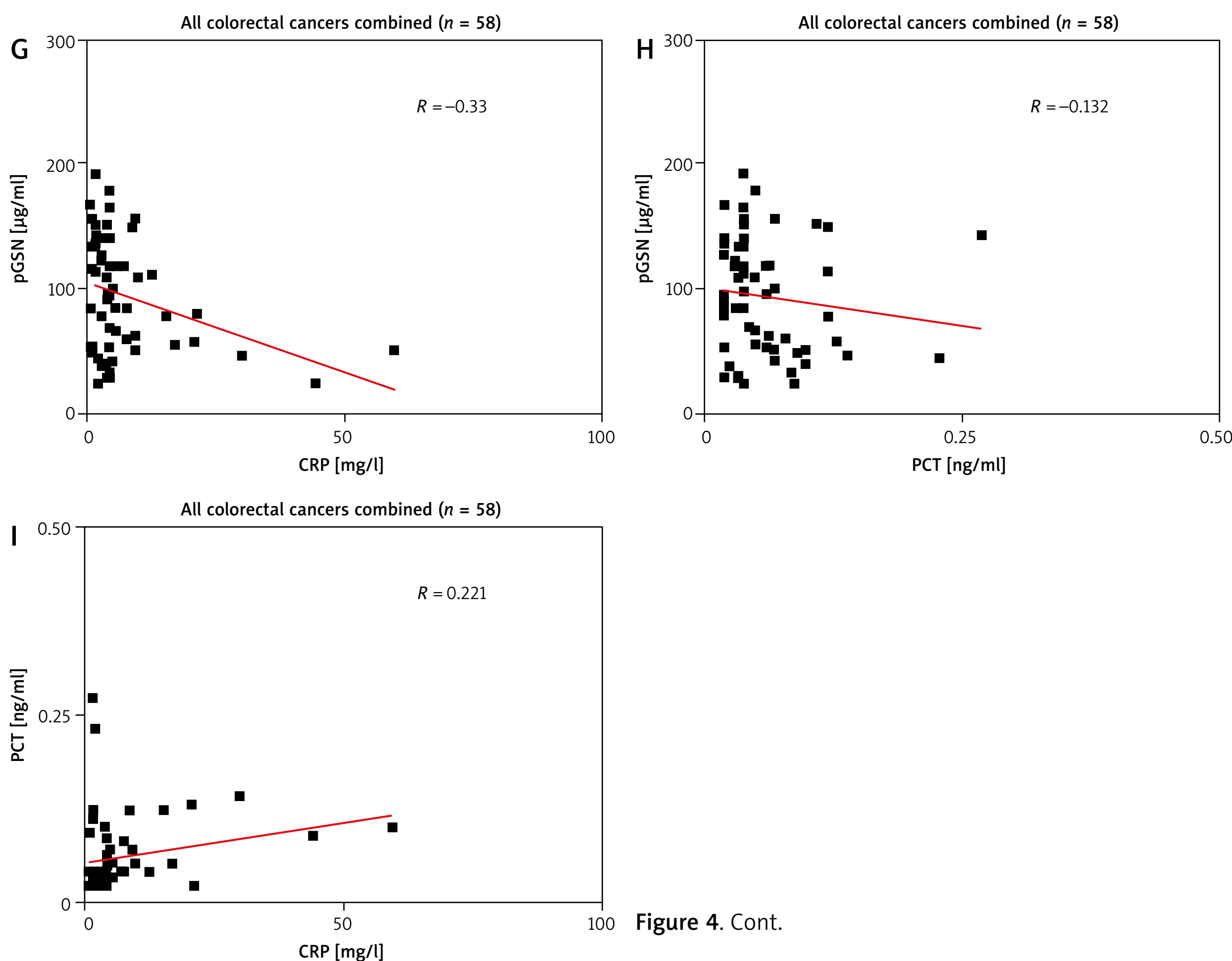

Figure 4. Cont.

and CRP levels that were positively correlated. Assuming that a decrease in the pGSN concentration not only indicates the development of inflammation, but also reflects a threat to the survival of cancer patients, the development of a diagnostic test that includes the evaluation of pGSN in a panel of inflammatory markers requires future research.

Conclusions

Our study has shown that the determination of pGSN levels in patients suffering from lung and colon cancers, in addition to traditional markers such as CRP and PCT, might have clinical value because all 3 markers are poorly correlated. Evaluating the plasma gelsolin concentration in the blood might help identify patients at higher risk of severe clinical outcomes when the elevated concentration of PCT is not sepsis related. Further studies involving more patients are needed to confirm our findings.

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Conflict of interest

The authors declare no conflict of interest.

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