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Procalcitonin testing for diagnosis and short-term prognosis in bacterial infection complicated by congestive heart failure: a multicenter analysis of 4698 cases

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Abstract

Introduction

Procalcitonin (PCT) is a biomarker for the clinical diagnosis of bacterial infection that is more specific and earlier than fever, changes in white blood cell count, and blood cultures. Congestive heart failure is an important cause of endotoxin resorption from the intestine, which significantly increases PCT expression in noninfected patients with heart failure. The diagnostic performance and cut-off value of PCT in patients with bacterial infection complicated by congestive heart failure needs to be confirmed.

Methods

A total of 4698 cases from different cities in China, including those with different classes of congestive heart failure, bacterial infection, bacterial infection complicated by heart failure and healthy individuals, were chosen for the diagnostic value analysis of PCT and screening candidate predictors of mortality in subjects with bacterial infection complicated by congestive heart failure.

Results

Patients with simple heart failure had significantly higher PCT levels than normal controls ($P < 0.01$), whereas patients with bacterial infection complicated by congestive heart failure had significantly higher PCT levels than those with simple infection ($P < 0.01$). Although it was useful for the diagnosis of infection (area under the ROC curve >80%), the positive predictive value of PCT decreased significantly with increasing severity of heart failure ($P < 0.05$), and the cut-off value of PCT concentrations for infection complicated by class-II, -III, and -IV heart failure were 0.086, 0.192 and 0.657 μg/L, respectively. Heart failure degree, PCT level, and age were the candidate predictors of mortality in patients with bacterial infection complicated by congestive heart failure.

Conclusions

These data suggest that complicated heart failure elevates the PCT level in patients with bacterial infection. Thus, the results of the PCT test must be analyzed correctly in consideration of the severity of heart failure. Close attention should be paid to cardiac function and PCT expression in aged patients with infection complicated by congestive heart failure.

Introduction

The differential diagnosis between sepsis and noninfectious systemic inflammatory response syndrome is of great importance to acutely ill patients because there might be an urgent need for changing the antimicrobial regimens already administered or surgical eradication of the septic foci. The difficulty is aggravated further by the ambiguous results of the cultures of different biological fluids and by the rapid progression to multiple organ dysfunction syndrome [1]. Various serological indices have been applied to help this situation. Limited specificity has been demonstrated for C-reactive protein (CRP) and interleukin (IL)-6, for

example, because their biosynthesis is triggered in infectious and noninfectious processes [2,3].

Procalcitonin (PCT) is a novel inflammatory marker of non-thyroid origin consisting of 116 amino acid residues. PCT levels are increased in the sera of patients with bacterial meningitis or sepsis [4-6], but are not elevated during viral infections or autoimmune disorders [7,8]. Despite PCT levels being increased in the serum 6 h after the intravenous administration of endotoxins in healthy volunteers [9], the exact locus of PCT production in sepsis is not known. Mirjam Christ-Crain and colleagues [10] support the use of PCT assessments to decide on the administration of antibiotics in infections of the lower respiratory tract. Researchers suggest that the PCT levels are normal if < 0.1 μg/L, and that PCT levels > 0.25 μg/L and > 0.5 μg/L are cutoffs for the consideration of, and starting antibiotic treatment, respectively [11,12]. However, the specific cutoff upon which this decision is based needs validation, particularly in other illnesses. Sandek et al. reported that the mean PCT level could reach 48 μg/L in negative cultures of blood, tracheal aspirates and urine of patients with more severe heart failure (e.g., cardiogenic shock) [13]. Therefore, clinical doctors must analyze and estimate the PCT level correctly in patients with bacterial infection complicated by congestive heart failure.

Materials and Methods

The study protocol was approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT). Written informed consent to be included in the study was provided by each patient.

Demographic study and pooled methodology

The samples from populations came from four cities in China: Guangzhou, Zhongshan, Wuhan and Beijing. The samples were from 6314 patients (age, 18–75 years) admitted to hospitals in these cities because of heart failure or infection and 446 healthy individuals undergoing health examinations. All four component data sets had comparable information available, including standard demographics, past medical history and drug therapy, presenting symptoms and signs, physical examination, results of serum chemistry tests, electrocardiography, and finally, the results of PCT and NT-proBNP testing. Glomerular filtration rate (GFR) was estimated using the modified diet in renal disease [14]. To determine the actual diagnosis, specially for heart failure patients, according to the guideline issued by New York Heart Association(NYHA), two independent cardiologists and physicians made the clinical diagnosis by reviewing all medical records(including echocardiographic data and laboratory results) pertaining to the patients, and these records were also cross reviewed by clinical doctors in different research components. Considering hematological changes were not specific, for bacteria infection, it can only be determined by blood and secretions culture. All the final diagnosis was established based on clinical datasheets and additional information obtained during hospitalization.

The patient groups were classified as: bacterial infection without heart failure (including septic shock in the advanced stage of infection); congestive heart failure without infection (heart failure only); and bacteria infection complicated by congestive heart failure (suffer from heart failure before bacterial colonization). Because it was hard to control mild and severe infection, and the physical response to bacterial infection is variated significantly

between every single person, samples with positive pathogenic bacteria culture were treated as a unified bacterial infection group. In order to avoid interference, patients with history of viral infections and autoimmune disorders, which could slightly elevate the PCT level in the serum, were excluded. What's more, samples in the control group were selected from healthy volunteers without hematological abnormality (including WBC, CRP, IL-6, NT-proBNP, etc). Those inconclusive subjects with negative bacterial culture and hematological abnormality were also excluded in this study. Even though infections can occur at any age, one study reported a transient increase in PCT expression in newborns and infants [15]. Low-age populations(<30 years old), which hardly experience heart failure, were avoided in the present study. Besides, due to the difficulty in obtaining accurate classifications and the substantial variability in data of class-I heart failure (asymptomatic heart failure), all samples were collected from patients with heart failure of class II–IV, which were classified according to guidelines set by the American College of Cardiology Foundation/American Heart Association. Those severe heart failure patients which with unavoidable renal dysfunction were evaluated by GFR . Although we have known that renal elimination of procalcitonin is not a major mechanism for procalcitonin removal from the plasma, and renal dysfunction will not severely influenced clinical diagnostic decisions [16], we still choose samples with high GFR. At last, of these complete and available data, 4698 cases reach consensus and were chosen for the further research, as shown in Table 1.

Table 1 Baseline demographics, results of physical examination, laboratory testing and clinical diagnosis of the 4698 study subjects categorized with respect to population center

Characteristics	Infection only (n = 1703)	Heart failure only (n = 1364)	Infection complicated by congestive heart failure (n = 1183)	Healthy Control (n = 448)
Physical examination				
Age (mean ± SD)	51.1 ± 10.3	57.9 ± 14.7	58.5 ± 11.4	57.1 ± 18.3
Male ratio (%)	51.7	48.3	49.4	50.0
Hypertension (%)	3.9	30.8	11.7	0
Chest pain (%)	2.4	33.7	18.6	0
Orthopnoea (%)	0	13.9	29.7	0
Cough (%)	41.6	7.8	23.3	0
Fever (%)	84.6	0.4	77.1	0
Laboratory tests				
GFR (mL/min/1.73 m^2) mean ± SD	71.7 ± 14.3	61.4 ± 18.2	64.1 ± 17.7	98.4 ± 5.5
WBC (10^9/L)	17.3 ± 9.7	7.4 ± 2.1	15.7 ± 8.0	7.8 ± 1.3
CRP(mg/L)	33.7 ± 19.6	11.7 ± 6.8	39.1 ± 18.4	4.7 ± 2.5
Blood culture positive (%)	39.3	0	22.7	0
secretion/hydrothorax culture positive (%)	60.7	0	77.3	0
NT-proBNP, mean ± SD	196 ± 127	8946 ± 4969	5116 ± 3777	45 ± 11
IL-6, mean ± SD	21.3 ± 15.1	7.3 ± 3.5	19.4 ± 11.9	2.6 ± 0.9

Follow-up for vital status among bacterial infection complicated by heart failure subjects was achieved utilizing hospital records as well as contact with caregivers or patients, when appropriate, through 22 days (the mean hospital stay of infection complicated by heart failure patients) from presentation.

PCT testing

PCT detection was conducted using a Roche Cobas E601 Electrochemiluminescence Immunoassay Analyzer (Roche, Basel, Switzerland) whose analytical performance has been confirmed to meet the request of experiment (Additional file 1). The calibration solution (batch numbers 167488 and 160068), analytical reagent (00162192), and quality control (QC) materials (16195300 and16195400) were purchased from Roche.

Comparative analysis of pct expression in different population groups

PCT levels of the specimens obtained from the normal population and patient populations with simple infection, simple heart failure, and infection complicated by heart failure, were compared and analyzed to identify the patterns of variation of PCT expression in different populations. The differential expressions of PCT in patients with simple heart failure relative to the normal control and that in patients with bacterial infection complicated by heart failure relative to simple infection were examined.

Comparative analysis of diagnostic performance of PCT using ROC Curves

A comprehensive analysis was conducted on the results of PCT detection with specimens from patients with simple bacterial infection and those with infection complicated by heart failure. The true-positive diagnostic cutoff of PCT was set to 1.0 and the true-negative diagnostic cutoff was set to 0.0, with 95% confidence intervals (CIs). The diagnostic performance of PCT for simple bacterial infection and infection complicated by heart failure was evaluated and the cutoffs were determined.

Short-term prognosis in bacterial infection complicated by congestive heart failure

Among 1182 infection complicated by congestive heart failure patients, 134 patients passed away in hospital or other medical centers within 22 days. The candidate predictors of mortality in subjects with bacterial infection complicated by heart failure were screened by COX regression analyses using sex, age, class of cardiac function, body temperature and commonly used hematological parameters (e.g., levels of PCT, WBC count, CRP, and IL-6) as independent variables. Although BNP and NT-proBNP were biomarkers which were wildly used in heart failure diagnosis, in our former work we found that they would be interfered by ischemic disease such as cerebral infarction [17]. So BNP and NT-proBNP were excluded as variables in the study.

Statistical analysis

Data analyses were carried out using SPSS ver19.0 (SPSS, Chicago, IL, USA). A test for normal distribution was done using the Kolmogorov–Smirnov method. Mean values that did not follow a normal distribution were compared using the Kruskal–Wallis H statistic. For pairwise comparisons, the level of significance was adjusted using the Bonferroni method. Diagnostic tests were assessed by ROC analyses. Predictors of mortality were screened out by COX regression using Forward Stepwise: Conditional method. $P < 0.05$ was considered significant.

Results

Expression patterns of PCT in different populations

PCT expression showed significant differences among the four population groups ($P < 0.05$) (Table 2). PCT levels were significantly higher in patients with simple heat failure than those in the normal control ($P < 0.05$), verifying the notion that heart failure can elevate PCT levels [13]. Patients with bacterial infection complicated by congestive heart failure had significantly higher PCT levels than those with simple bacterial infection, suggesting that heart failure may influence a PCT-based diagnosis of infection, as shown in Figure 1.

Table 2 Comparison of PCT expression according to population

Group	PCT						
	Median	Interquartile range	Mean rank	χ^2 (Overall)	P (Overall)	χ^2 (Group)	P (Group)
Simple infection	0.28	0.06-0.49	1661.01	446.9	0.00	(12) 52.7	(12) 0.00
						(13) 233.8	(13) 0.00
						(14) 77.6	(14) 0.00
Simple heart failure	0.13	0.05-0.22	1288.63			(23) 252.9	(23) 0.00
						(24) 9.10	(24) 0.00
Infection complicated by congestive heart failure	0.45	0.12-2.59	2232.60			(34) 205.7	(34) 0.00
Healthy control	0.04	0.05-0.12	996.42				

Figure 1 Differential expression of PCT in different populations.

Comparison of the diagnostic performance of PCT for simple bacterial infection and infection complicated by congestive heart failure

In accordance with manufacturer instructions and the literature [5], we chose 0.1 μg/L as the cutoff for comparing the diagnostic value of PCT among different populations. PCT was used for the diagnosis of infections, so a comparative analysis was undertaken on patients with simple bacterial infection and those with infection complicated by congestive heart failure. At the fixed PCT level of 0.1 μg/L, the diagnostic sensitivity of PCT was significantly higher for infection complicated by heart failure than for simple infection, whereas the corresponding positive predictive value of PCT was significantly lower for the former than for the latter population (Table 3). The positive predictive value of PCT decreased significantly with increasing severity of heart failure ($P < 0.05$). Nevertheless, PCT has a certain diagnostic value for simple bacterial infection and infection complicated by heart failure (class II–IV) (area under the ROC curve (AUC) > 80%) (Figure 2). The diagnostic cutoffs of PCT for patients with class-II, -III, and -IV heart failure increased significantly with the severity of heart failure, i.e., 0.086, 0.192 and 0.657 μg/L, respectively (Figure 3).

Table 3 Comparison of PCT diagnosis between simple infection and different classes of infection complicated by congestive heart failure

Class	Cutoff (μg/L)	Sensitivity	Youden index	Positive predicative value	Negative predicative value	Accuracy	Z	*P*
Simple infection	0.1	56.3	0.284	95.1	14.7	57.8	11.345	<0.05
Infection complicated by class II heart failure	0.1	76.6	0.487	90.9	45.7	75.6	20.232	<0.05
Infection complicated by class III heart failure	0.1	78.4	0.505	87.6	57.1	76.6	20.168	<0.05
Infection complicated by class IV heart failure	0.1	87.2	0.593	68.6	89.0	78.3	16.518	<0.05

Figure 2 ROC curve for the PCT diagnosis of simple infection and infection complicated by congestive heart failure. The area under the ROC curve is above 80%, which means PCT still has the diagnostic value for simple bacterial infection and infection complicated by congestive heart failure. **A.** Diagnostic curve of PCT for simple bacterial infection. **B**. Diagnostic curve of PCT for infection complicated by congestive heart failure;

Figure 3 ROC curve for PCT based diagnosis of infection when patients complicated by different classes of heart failure. As depicted, PCT had high AUC in each heart failure group. However, the best cutoff values for each group were different.

Short-term prognosis in patients with infection complicated by congestive heart failure

Sex, age, body temperature, levels of PCT, WBC, CRP and IL-6, and class of cardiac function were used as the independent variables for COX regression analyses and screened using the Forward Stepwise: Conditional method. Finally, three factors were screened and included in the equation: age, PCT level, and class of cardiac function. The chi-square test of the model produced $\chi^2 = 73.393$ ($P < 0.01$), which means there were statistical differences in this model. The impact factors included in the equation are shown in Table 4. Age, PCT level, and cardiac function were the candidate predictors of mortality, with relative risk (RR) of 1.061 times (1.006-1.119), 1.110 times (1.053-1.170), and 2.719 times (1.319-5.605), respectively. The cumulative survival function at mean of covariates was shown as Figure 4.

Table 4 Candidate predictors of mortality in subjects with infection complicated by heart failure, based on 134 cases

Factors	B	SE	Wald	df	Sig.	RR	RR.95.0% CI	
							Lower	Upper
Age	0.059	0.027	4.734	1	0.030	1.061	1.006	1.119
Cardiac functional class	1.000	0.369	7.343	1	0.007	2.719	1.319	5.605
PCT level	0.104	0.027	15.047	1	0.000	1.110	1.053	1.170

*RR: With one-year increase in age, the possibility of death increases by 1.061-times; as compared with that of patients with PCT < 0.1, the possibility of death increases by 1.11-times in those with PCT > 0.1; with one-class increase in the cardiac function, the possibility of death increases by2.719-times.

Figure 4 Cumulative survival function at mean of covariates for survival analysis in infection complicated by congestive heart failure during 22 days hospitalization. Horizontal axis means survival time (days), and vertical coordinate means the probability of survival at the corresponding times. This is a decline curve, which means steeper the curve is, and shorter the survival time will be. The slope indicates the death rate.

Discussion

PCT is a peptide precursor of calcitonin which, has been commonly used for the early diagnosis of sepsis, differential diagnosis between bacterial and viral infections, and antibiotic guide in clinical treatment [18]. However, from this retrospective analysis, the results showed that patients with simple heart failure had significantly higher levels of PCT than the normal control, whereas subjects with bacterial infection complicated by heart failure had significantly higher levels of PCT than those with simple bacterial infection. The diagnostic performance of PCT in patients with bacteria infection complicated by heart failure needs to be reconsidered, and the cutoff value should be confirmed.

Sandek et al. [13] found that heart failure interferes with the PCT-based diagnosis of infection. The authors stated that the diagnostic cutoff of PCT should be established in various disease states. Despite the necessity of the diagnostic cutoff, there are some main difficulties remain, such as lack of specific standards and exclusion standards, no clinical manifestations differences between systemic and nonsystemic infections, and difficulty in experimental conditions controlling, et al. To ensure that the experimental conditions were consistent, in our multicenter study, the samples with consensus diagnosis were collected and processed, and we undertook the tests using reagents from the same manufacturer. Laboratories, which take part in this subject, have accepted and gone through the external quality assessment initiated by National Ministry of Health Department, and the precision and accuracy of detection have been verified to complied with the requirements of the clinical test.

The findings in this study have suggested that heart failure may interfere with PCT expression. However, PCT detection was still found to be useful in the diagnosis of bacterial infection complicated by heart failure(AUC > 80%) and the diagnostic sensitivity increased with the severity of heart failure. This dose not prove that PCT is conducive to the diagnosis but, in diagnosed patients with infection, complicated heart failure increased their PCT levels, thereby increasing the diagnostic sensitivity. This factor is also a main cause why the positive predictive value of PCT decreases with the severity of heart failure. Heart failure can affect the PCT level, so the diagnostic cutoff value of PCT needs to be altered accordingly. We showed that the PCT level increased significantly with increasing severity of heart failure in noninfected patients, and that the cutoff concentration of PCT was up to 0.657 μg/L in patients with simple class-IV heart failure. These observations suggest that clinical doctors should consider the severity of heart failure during the diagnosis of a specific infection. We have to mention that, the PCT level in some patients of infection group was not that high. However, as far as PCT level in bacterial infection concerned, there might be two reasons. First, the PCT level in patients with gram positive bacterial is much lower than that in patients with gram negative bacterial infection [19]. Second, inflammatory mediators such as IL-1β, TNF-α, and IL-6, which could elevate serum PCT level, in some aged patients, specially those with poor immune response and were suffered from early stage of local infection, might not be induced as soon as bacteria colonization [20,21].

In patients with heart failure, infections (especially pulmonary infections) can cause continuous progression of the disease *via* complementary pathogenic mechanisms. In contrast, deaths of patients with simple heart failure or myocardial infarction are rare. In this short-term prognosis analysis, the three infection-screening markers commonly used in medical laboratories (WBC count, CRP, IL-6) were not chosen as candidate predictors of mortality.

These three factors may lack specificity for the diagnosis of infection complicated by heart failure. In particular, a considerable number of the infected patients without fever had no increases in the WBC count [22]. CRP acts as a "stress protein", and can not be used to prove infection is present. Despite reports on its diagnostic application, IL-6 lacks specificity in the diagnosis of viral and bacterial infections [23]. Continuous aging will cause decline of cardiac function to varying degrees. However, the decline in cardiac function will inevitably decrease in the circulatory function of the whole body, and promote the constant sorption of endotoxins into the bloodstream, leading to an elevation of PCT levels. Additionally, functional decline will induce a series of infections, posing a synergistic promotion effect on the elevation of PCT expression. Therefore, close attention should be paid to the age, severity of heart failure, and PCT level in the treatment of patients with bacterial infection complicated by heart failure.

Conclusion

Heart failure is a common factor that interferes with PCT diagnostic value in bacterial infection. The laboratory data of patients with bacterial infection complicated by congestive heart failure should be comprehensively analyzed and a complete clinical nursing program should be adjusted. Presently, the clinical diagnosis of infection is primarily experience-based, and specific classification criteria are lacking. The diagnosis and classification of early infection with collaborative applications of effective infection markers remain the focus of clinical research.

Key messages

- PCT level increased significantly with increasing severity of heart failure in noninfected patients.
- PCT has a certain diagnostic value for simple infection and infection complicated by heart failure (class II–IV) (area under the ROC curve (AUC) > 80%), however, the positive predictive value of PCT decreases with the severity of heart failure.
- The diagnostic cutoffs of PCT for patients with class-II, -III, and -IV heart failure increased significantly with the severity of heart failure, i.e., 0.086, 0.192 and 0.657 μg/L, respectively
- Age, PCT level, and cardiac function were the candidate predictors of mortality, with relative risk (RR) of 1.061 times (1.006-1.119), 1.110 times (1.053-1.170), and 2.719 times (1.319-5.605), respectively.
- In order to prolong the survival time, the laboratory data of patients with infection complicated by congestive heart failure should be comprehensively analyzed and a complete clinical nursing program should be adjusted.

Abbreviations

CRP, C-reactive protein; CV, Coefficient of variability; GFR, Glomerular filtration rate; IL-6, Interleukin 6; NT-proBNP, Amino-terminal pro-brain natriuretic peptide; PCT, Procalcitonin; SD, Standard deviation; WBC, White blood cell

Competing interests

All authors have no competing interests regarding this paper.

Authors' contributions

Weijia W and Xiuming Zhang developed the study design and coordinated its implementation. Na G, Jing L, Huimin Y, Wei L and Peng Z were responsible for patient recruitment as well as data collection and they carried out the statistical analysis. Dongmei W participated in interpretation/discussion of results and drafted and revised the manuscript. All authors read and approved the final manuscript.

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Additional file

Additional_file_1 as DOC

Additional file 1 Verification of the precision and accuracy of PCT detection

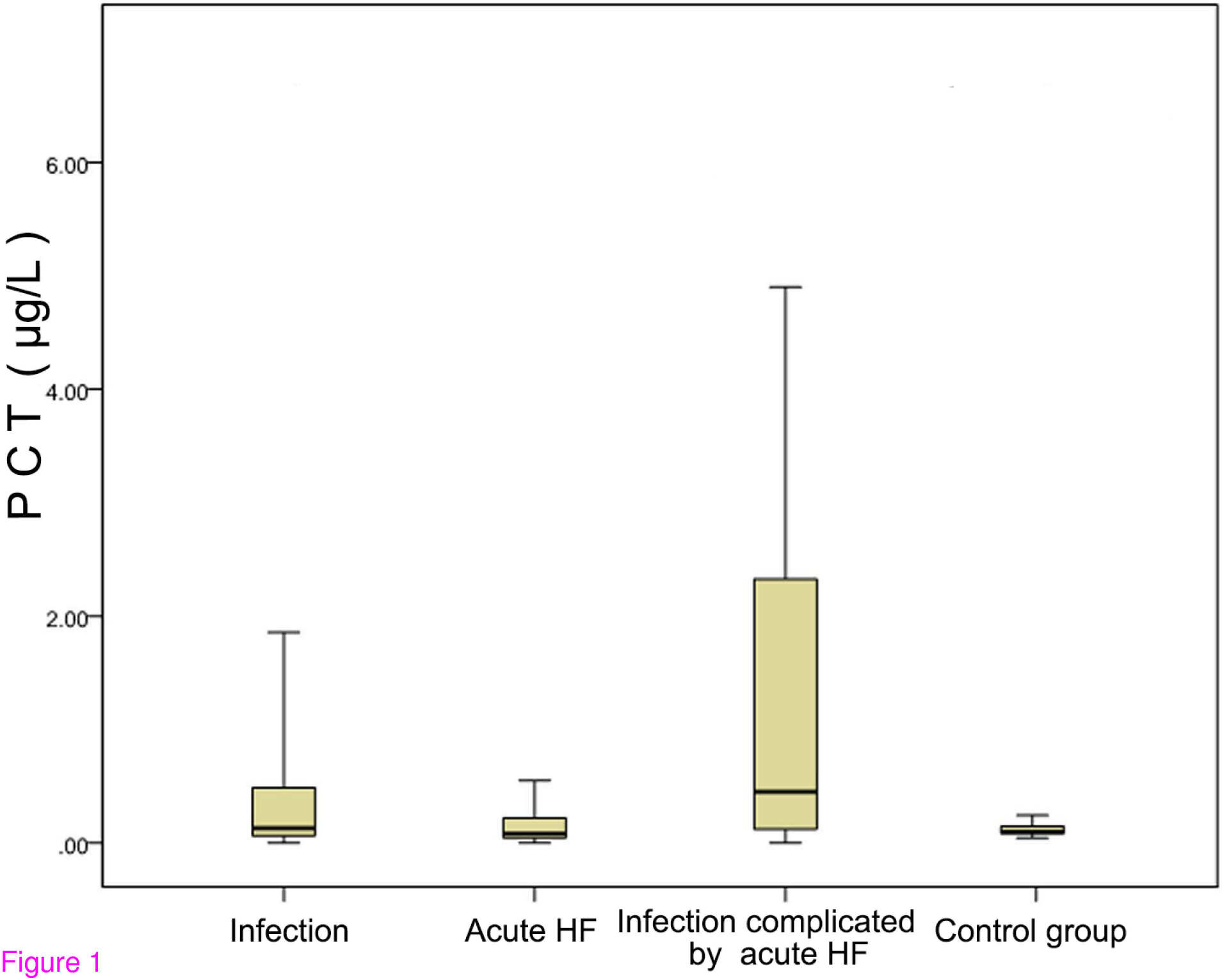
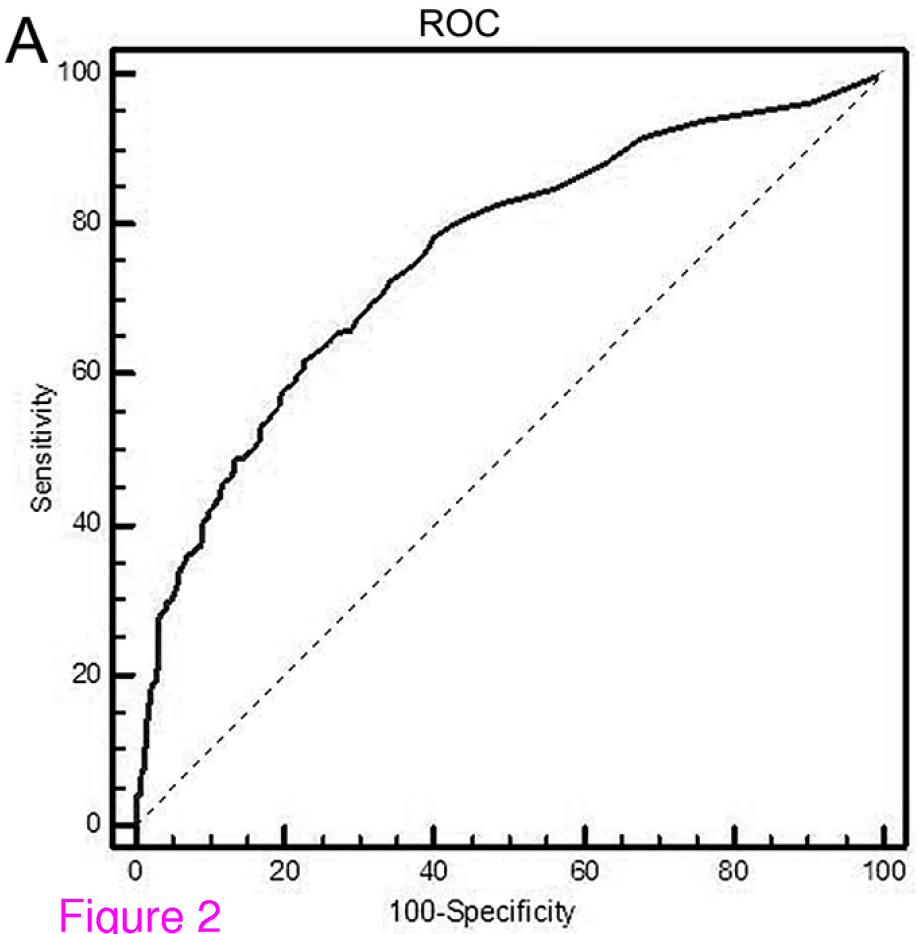

6.00
4.00
2.00
.00
PCT (μg/L)
Infection
Acute HF
Infection complicated by acute HF
Control group

Figure 1


A
ROC
Sensitivity
100-Specificity
0
20
40
60
80
100

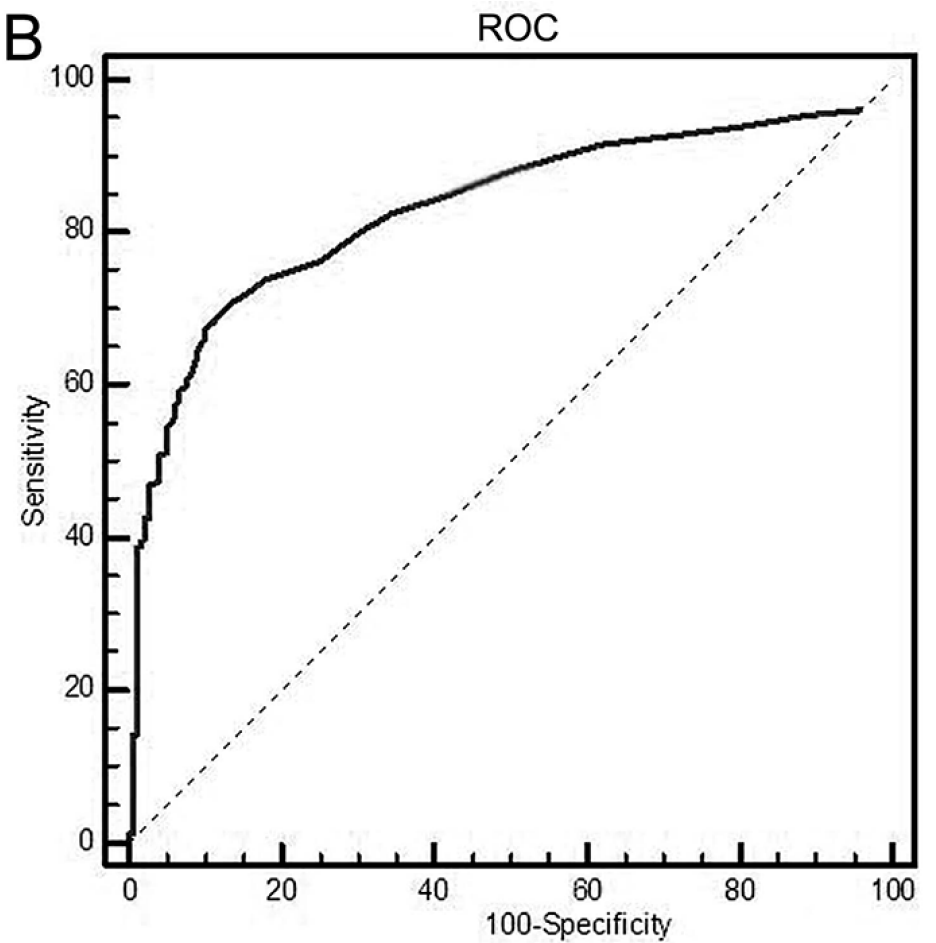

B
ROC
Sensitivity
100-Specificity
0
20
40
60
80
100

Figure 2

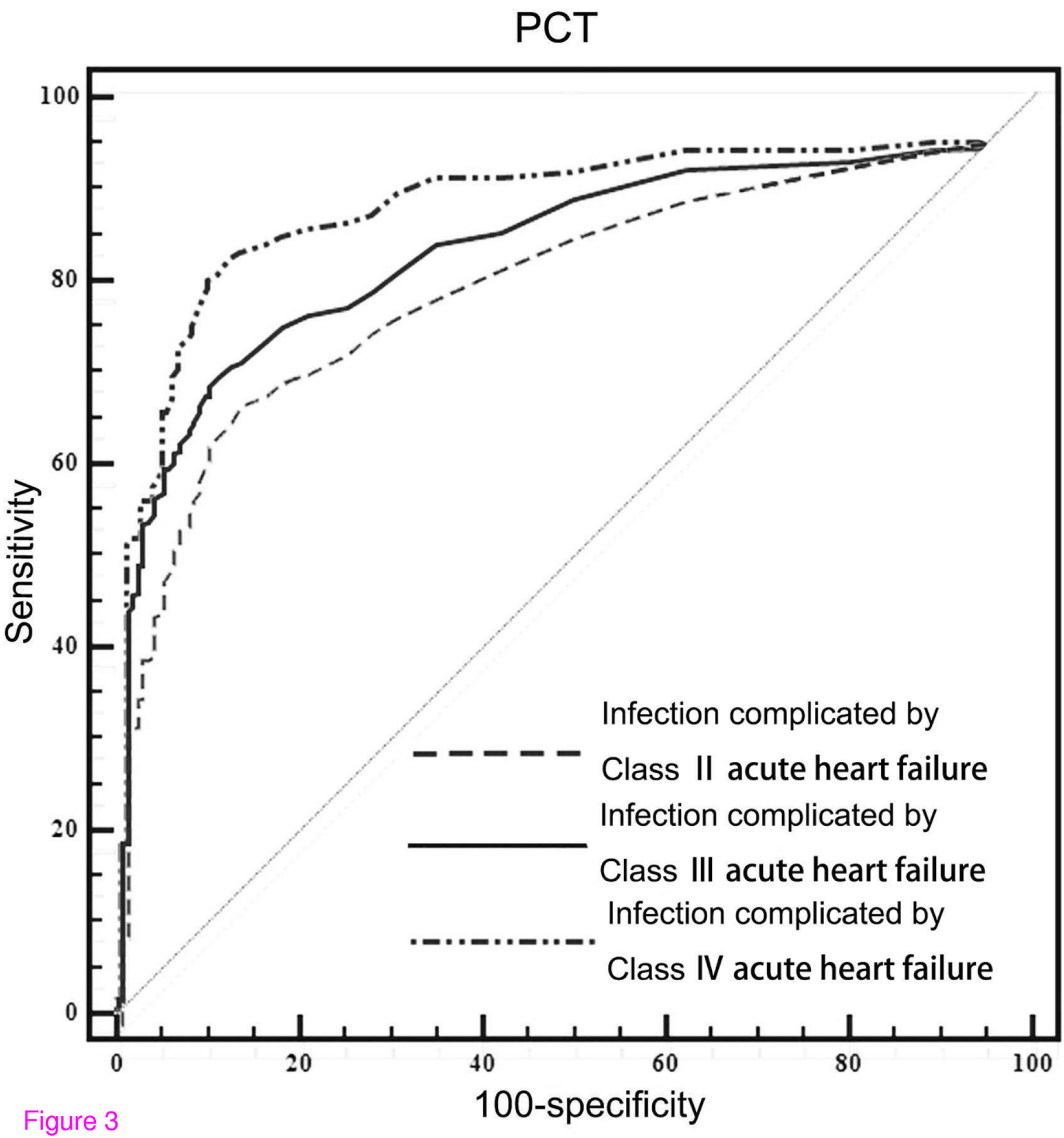

PCT
Sensitivity
100-specificity
0
20
40
60
80
100
Infection complicated by
Class II acute heart failure
Infection complicated by
Class III acute heart failure
Infection complicated by
Class IV acute heart failure

Figure 3

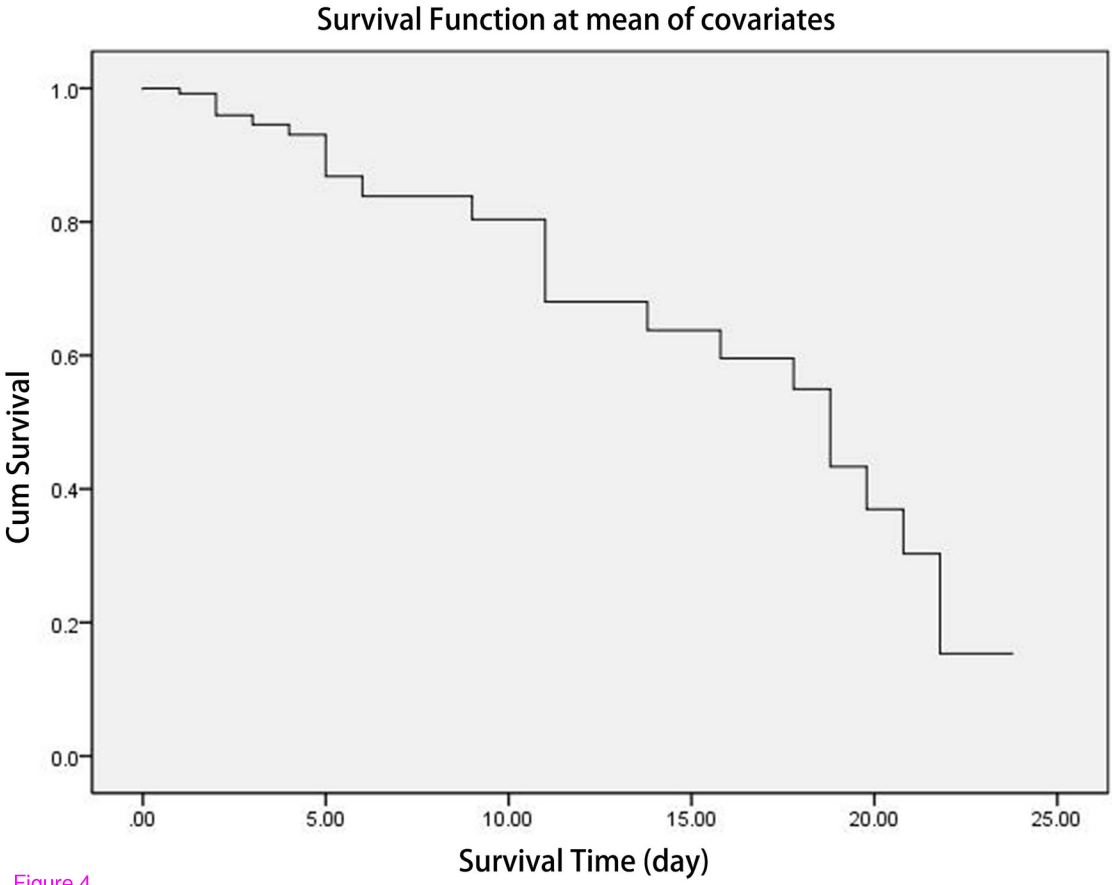

Survival Function at mean of covariates
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.00
5.00
10.00
15.00
20.00
25.00
Survival Time (day)

Figure 4

Additional files provided with this submission:

Additional file 1: 1652277528105477_add1.doc, 40K
http://ccforum.com/imedia/1325545081177660/supp1.doc

Procalcitonin-guided antibiotic treatment in heart failure

Sir—Mirjam Christ-Crain and colleagues[1] support the use of procalcitonin assessments to decide on the administration of antibiotics in lower respiratory tract infections (Feb 21, p 600).[1] The authors suggest that procalcitonin concentrations are normal when less than 0·1 μg/L, and that concentrations of more than 0·25 μg/L and 0·5 μg/L are cut-offs for consideration of and starting antibiotic treatment, respectively.[1] However, the specific cut-off, on which this decision is based, needs validation particularly in other illnesses.

Raised procalcitonin concentrations are regarded as a valid marker for bacterial sepsis,[2] although concentrations rise after injection of bacterial endotoxin even in healthy individuals.[3] Thus, procalcitonin indicates endotoxaemia, which is due to infection in many cases, but not in all.

Since heart failure is a very frequent cause of dyspnoea in the accident and emergency department, we argue that patients with congestive heart failure might have been underrepresented in the study by Christ-Crain and colleagues. In the procalcitonin group, 24 patients with congestive heart failure were not deemed eligible for the study. However, in a recent investigation by Niebauer and coworkers,[4] patients with congestive oedematous heart failure were shown to have slightly raised mean procalcitonin concentrations of 0·145 μg/L (SD 0·94 μg/L), compared with controls. Patients with heart failure are assumed to have altered gut permeability, owing to bowel congestion or ischaemia, which leads to invasion of bacterial endotoxins.

Since the procalcitonin assay used in this study had a lower functional assay sensitivity (0·3 μg/L) than the assay used by Christ-Crain and colleagues (0·06 μg/L), there could be even higher procalcitonin concentrations in patients with heart failure than those found by Niebauer and colleagues. In more severe states of heart failure, such as cardiogenic shock, we have noted mean procalcitonin concentrations of 48 μg/L with negative cultures of blood, tracheal aspirates, and urine.[5] Patients with heart failure would benefit from early detection of bacterial infection since they are prone to lower-airway infections. Further studies are needed to confirm the use of procalcitonin to predict usefulness of antibiotic therapy, and more work is required to validate specific cut-offs in different disease settings.

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Authors' reply

Sir—We are grateful to Anja Sandek and colleagues for highlighting important points discussed in our paper. Circulating procalcitonin concentrations are similarly heightened in gram-positive and gram-negative infections.[1] Thus, endotoxin (lipopolysaccharide) is only one of several inducers of procalcitonin secretion. Accordingly, proinflammatory cytokines—eg, interleukin 1b, tumour necrosis factor α, and interleukin 6—induce and augment lipopolysaccharide-induced procalcitonin expression and secretion.[2] Conversely, interferon gamma, released during viral infections, attenuates interleukin 1b-induced procalcitonin production in human cells. These findings might explain why procalcitonin is superior to other clinical and laboratory markers for diagnosing clinically relevant bacterial respiratory tract infections, as shown in our study.

As Sandek and co-workers correctly state, raised procalcitonin concentrations can be identified in several non-infectious diseases.[3] In this respect, high procalcitonin concentrations during cardiogenic shock indicate bacterial challenge of the host after bacterial translocation during intestinal hypoperfusion. This bacterial challenge can lower the specificity, but not the sensitivity, of procalcitonin for the diagnosis of bacterial lower respiratory tract infections. In our study, 18 (7·4%) patients with lower respiratory tract infection as their main diagnosis had congestive heart failure. The presence of congestive heart failure did not result in heightened procalcitonin concentrations, assessed by a sensitive assay (Kryptor PCT, functional assay sensitivity 0·06 μg/L). Unfortunately, in the studies cited by Sandek and co-workers, an insensitive procalcitonin-assay was used (LUMITest PCT, 0·5 μg/L), which does not reliably measure the concentrations reported. In addition, negative culture results do not exclude a concomitant infection. To resolve this important question, we started a prospective study to correlate circulating brain natriuretic peptide and procalcitonin concentrations in patients with respiratory tract infections.

The diagnostic accuracy of procalcitonin and its optimum cut-offs are completely dependent on use of a sensitive assay in an appropriate clinical setting. In a medical intensive care unit, for example, a cut-off of 1 μg/L was shown to be reliable for the diagnosis of sepsis.[1] Most sepsis is caused by pulmonary infections. In this context, bacterial lower respiratory tract infections can be viewed as sepsis precursors. Accordingly, the cut-off of procalcitonin to detect bacterial respiratory tract infections must be lowered.

We have chosen cut-offs based on studies by our group[1] and others.[4,5] The reliability of our cut-off range of 0·1–0·5 μg/L is shown by the similar outcome of the two groups, despite the striking reduction of antibiotic use in the procalcitonin-guided group.

Procalcitonin is not a substitute for a careful history and physical examination. However, as a surrogate marker it provides important additional information, and questions currently used gold standards for the clinical diagnosis of bacterial lower respiratory tract infections. Specifically, procalcitonin is also a sensitive tool in the presence of co-morbidities—eg, congestive heart failure.

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Attitudes towards delivering bad news in Peru

Sir—It is clear from Lesley Fallowfield and Valerie Jenkins' Review on delivering bad news in medicine (Jan 24, p 312),[1] that there is a conflict of ethical principles. Physicians must choose between the patient's right to be fully informed (autonomy) and the relatives' request to avoid further emotional distress by concealing information.

We would like to share our own findings from a semi-structured interview done at Daniel Carrion Hospital, Callao, Peru.

We interviewed 42 patients and 30 accompanying relatives, independently but simultaneously, before a diagnostic endoscopy. Patients were asked whether they would want to know if a tumour were found, and relatives were asked whether they wanted their family member to be informed of such a diagnosis. 38 (91%) patients interviewed desired to be told their diagnosis, whereas only 17 (57%) of their relatives wanted the diagnosis to be disclosed. The main reasons for patients wanting to be informed (more than one answer was permitted) were: "would like to seek treatment", 31 (82%); "making personal arrangements", eight (21%); "it is the patients' right", eight (21%); and "to be able to say goodbye", four (11%). The main reason given by the relatives for concealing the diagnosis from the patients was: "to avoid emotional distress for the patient", 13 (100%).

Finally, we interviewed 31 physicians involved in the care of cancer patients. Faced with the dilemma of following the patient's or the relative's desire, 14 (45%) were in favour of not telling patients their diagnosis and informing the relatives instead. The main reasons for not informing the patient were: "to avoid an emotional shock that could deteriorate the patient's condition", 13 (93%); "because it is a family responsibility", seven (50%); and "to preserve hope", four (29%).

We believe this is a good example of how physicians in our country act on the principle of bioethics even to the detriment of patients' autonomy.

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Fetal alcohol syndrome

Sir—In March 2004, the UK government introduced an alcohol reduction strategy with the ambition to address the binge-drinking culture.[1] The report highlights the facts that nearly one in five women drink more than the recommended limit, 13% of women drink on five or more days per week, and women aged between 16 and 24 years are more likely than all other age-groups to binge drink. Furthermore, binge drinking accounts for 22% of all drinking episodes in women.

The report notes the major burden of alcohol on general health and society, but fails to draw attention sufficiently to the issue of teratogenic alcohol effects on the fetus and long-term implications for the individual and society.

The Australian National Alcohol Strategy,[2] by contrast with this government report, estimates that the recorded prevalence of fetal alcohol syndrome (FAS) around the world is, on average, 1 per 1000 livebirths; the reported prevalence in more recent studies of fetal alcohol effects, fetal alcohol spectrum disorder, and alcohol-related neurodevelopmental disabilities is 9·1 per 1000 livebirths.[2,3] This high rate contrasts with figures from parts of Europe where prevalence is estimated to be around 0·08 per 1000 livebirths. These findings suggest a substantial underestimate of the prevalence of FAS, and associated disorders, within the UK.

Maier and West[4] have suggested that there is an important link between large rises in blood alcohol levels and subsequent precipitous withdrawal (as occurs in binge drinking) in the pathogenesis of FAS. The striking and sudden diminutions in alcohol concentrations in the blood and central nervous system seem to cause apoptotic damage to developing neurons and other cells.[4] The timing of the drinking can further affect which features of FAS are seen. Facial stigmata might be absent, yet marked behavioural features can result owing to differing vulnerable periods during fetal development.[3] This variation makes diagnosis difficult. Currently, children and adults affected by FAS have no specific service to which they can relate; yet, they remain highly vulnerable to psychiatric, psychological, behavioural, educational, social, and forensic difficulties (ie, difficulties in learning from the consequences of ones actions).[3]

There have been several publications estimating the cost of FAS to society. Klug and Burd calculated the 20-year financial price of each person with FAS to be close to US$500 000;[5] however, FAS is preventable.

The dangers of smoking during pregnancy continue to be emphasised. We argue that further research into FAS and alcohol-related neuro-developmental disabilities, in the UK and elsewhere, is urgently needed to raise awareness, enhance diagnosis and multiagency support, and improve intervention for people of all ages who have this lifelong debilitating disorder. We urge for greater public information about the harmful effects of alcohol during pregnancy, especially in light of the reported prevailing patterns of alcohol consumption. We believe these steps are needed, without delay, to prevent a potential epidemic of long-term profound and multiple neuro-developmental disabilities with all the associated negative individual, familial, societal, and financial implications.

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