Original Article

Retrospective study on prognostic importance of serum procalcitonin and amino-terminal pro-brain natriuretic peptide levels as compared to Acute Physiology and Chronic Health Evaluation IV Score on Intensive Care Unit admission, in a mixed Intensive Care Unit population

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ABSTRACT

Background: Timely decision making in Intensive Care Unit (ICU) is very essential to improve the outcome of critically sick patients. Conventional scores like Acute Physiology and Chronic Health Evaluation (APACHE IV) are quite cumbersome with calculations and take minimum 24 hours. Procalcitonin has shown to have prognostic value in ICU/Emergency department (ED) in disease states like pneumonia, sepsis etc. NTproBNP has demonstrated excellent diagnostic and prognostic importance in cardiac diseases. It has also been found elevated in non-cardiac diseases. We chose to study the prognostic utility of these markers on ICU admission. **Settings and Design:** Retrospective observational study. **Materials and Methods:** A Retrospective analysis of 100 eligible patients was done who had undergone PCT and NTproBNP measurements on ICU admission. Their correlations with all cause mortality, length of hospital stay, need for ventilator support, need for vasopressors were performed. **Results:** Among 100 randomly selected ICU patients, 28 were non-survivors. NTproBNP values on admission significantly correlated with all cause mortality (P = 0.036, AUC = 0.643) and morbidity (P = 0.000, AUC = 0.763), comparable to that of APACHE-IV score. PCT values on admission did not show significant association with mortality, but correlated well with morbidity and prolonged hospital length of stay (AUC = 0.616, P = 0.045). **Conclusion:** The current study demonstrated a good predictive value of NTproBNP, in terms of mortality and morbidity comparable to that of APACHE-IV score. Procalcitonin, however, was found to have doubtful prognostic importance. These findings need to be confirmed in a prospective larger study.

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INTRODUCTION

Scores such as Acute Physiology and Chronic Health Evaluation-II (APACHE-II), or APACHE-IV for prognostic implications are calculated based on the worst values of parameters in the first 24 h of admission.

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There is a dire need to develop a system which will help us in early identification of patients at risk of rapid deterioration so that timely intervention may be done.

Procalcitonin (PCT) is a 14 kd protein, produced by thyroid C-cells physiologically, extrathyroidal production of PCT in inflammatory conditions. It is stable in samples, its assay is relatively easy to perform, with a moderate cost and with early result availability. PCT has been extensively studied for diagnostic and prognostic purposes in the emergency department and Intensive Care Unit (ICU) for many diseases like community-acquired pneumonia, sepsis, bacterial meningitis, etc., Studies have, however, shown conflicting results. But there is an indication that it is potentially a biomarker of a state or systemic inflammatory response syndrome/sepsis/severe sepsis, and not an indicator of a disease *per se*.[1,2]

Brain natriuretic peptide (BNP) is a neurohormone produced by the cardiac ventricles in response to pressure or volume overload.[3] BNP is primarily a pro-hormone, which produces the active BNP and the inactive amino terminal (NT) proBNP molecules. Plasma concentration of both these peptides can be measured and have comparable diagnostic and prognostic accuracy.[4] In heart failure patients, NTproBNP is an established prognostic marker for increased cardiovascular and all-cause mortality.[5] NTproBNP is also found elevated in noncardiac conditions. It has been found to predict mortality in patients with pulmonary embolism, sepsis, and shock.[3]

A retrospective analysis was conducted to study the utility of PCT and NTproBNP for early risk stratification in ICU with the aim of studying their predictive value for mortality, need for vasopressors and ventilatory support as compared to conventional scores like APACHE-IV.

MATERIALS AND METHODS

The analysis was conducted in 2012–2013 after approval from the Ethics Committee. A retrospective search of eligible patients was accomplished using the hospital information system. The eligible population comprised of ICU patients admitted between November 2009 and October 2012. All those patients who were >18 years of age, had an ICU stay of >24 h, and had PCT and NTproBNP measurements on ICU admission were included. The markers had been ordered on the primary team's discretion.

Serum PCT estimation was done by enzyme-linked fluorescent assay technique using VIDAS PCT automated qualitative test on VIDAS instruments with human sera/plasma (lithium heparinate). The assay principle combines a one-step immunoassay sandwich method (Biomeriux, SA) with a final fluorescent detection in the wells containing anti-PCT antibodies labeled with alkaline phosphatize (conjugate). The concentrations were expressed in nanograms per milliliter, values >0.05 ng/ml were considered positive. Quality control was done routinely with the control kits in each VIDAS PCT kit.

Serum NTproBNP level assay was done by immunometric technique using Johnson analyzer VITROS-5600, wherein biotinylated antibody (sheep anti-NTproBNP) and horseradish peroxidise - labeled conjugate (sheep anti-NTproBNP) are used to complex with the substrate, which in turn, is measured by luminescent reaction (immunodiagnostic system). The levels are expressed in picograms per milliliter, with biological reference range for under 75 years age as 125 pg/ml and for above 75 years as 450 pg/ml; performance specification 5.00–35000 pg/ml.

The information was recorded for the entire cohort in terms of age, sex, hospital discharge state (dead or alive), reason for ICU admission (medical or surgical), pre-existing comorbid diseases, duration of hospital stay, duration of ICU stay, need for vasopressors, need and duration of mechanical ventilation, need for invasive monitoring, APACHE-IV score, PCT and NTproBNP levels on admission in ICU. Sepsis was defined as the presence (probable or documented) of infection together with systemic manifestations of infection as per the Surviving Sepsis Guidelines 2012.[6] Chronic kidney disease was defined as kidney damage for three or more months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate, manifested by pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests.[7] Cirrhosis or chronic liver disease was considered based on the history, and if imaging showed nodularity or distortion of liver architecture. A diagnosis of chronic obstructive pulmonary disease (COPD) was confirmed when a patient had symptoms of COPD and was found to have airflow obstruction on clinical examination. Diagnosis of pneumonia was based on symptoms and signs of lower respiratory tract infection in a patient with supportive chest X-ray findings. Cerebrovascular accident (CVA) or stroke was defined as an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 h or until death.[8] Postoperative patients were mainly elective

otorhinologic surgical and emergency peripheral vascular surgical patients.

Statistical analysis

Categorical variables were expressed as a percent and continuous variables as mean, median, range and standard deviation. Group comparisons and univariable correlations between different groups were made for equality of variances. Statistical significance was defined as $P < 0.05$ in all analysis. Receiver operating characteristic statistics (ROC) curves of independent prognostic determinants of mortality and morbidity were evaluated. Statistical comparison between the area under the curve (AUC) of different parameters was calculated. Effects of variables on mortality and morbidity were examined by logistic regression analysis. Optimal cutoff values were identified by determining the minimal value for $(1 - \text{Sensitivity})^2 + (1 - \text{Specificity})$.[2]

RESULTS

During the study period, 100 patients were found to be eligible for enrolment. The mean age of the population was 60.28 years; median age was 63 years (range 18–95 years). Sixty-three were males and 37 patients were females. Primary reason for admission to ICU was medical in 93 patients, and seven were postoperative patients. Among medical patients, 39 patients were admitted with sepsis, two patients had decompensated chronic liver disease, ten patients had acute on chronic kidney disease, thirty patients had an acute exacerbation of COPD and pneumonia, and 12 patients were admitted with CVAs. Among the chronic medical conditions, 59 patients had hypertension, forty patients had diabetes, forty patients had underlying coronary artery disease, two patients had chronic liver disease, 12 patients had underlying chronic kidney disease, 28 patients had COPD, and nine patients had the underlying peripheral vascular disease.

An average APACHE-IV score of the entire cohort was 64.14, with a median of 61. Average PCT concentration was 9.04 ng/ml and median was 1.4 ng/ml. Mean NTproBNP concentration was 13327.7 pg/ml and median was 6485 pg/ml. Mean hospital stay and ICU stay (in days) were 20.32 and 12, with median of ten and nine, respectively. Sixty-two patients required vasopressors and 72 patients required ventilatory support during their hospital stay [Table 1].

There was a significant difference among the survivors and nonsurvivors in terms of morbidity (need for

Table 1: Baseline clinical characteristics, clinical variables, and outcome of subjects

Patient characteristics	Number
Number of patients	100
Age (years)	
Range	18-95
Median	63
Mean	60.28
Gender	
Men	63
Women	37
Reason for admission	
Medical	l93
Surgical	17
Principal diagnosis	Sepsis 39
	Respiratory failure (AE-COPD, pneumonia)
	CVAs 12
	Renal insufficiency 10
	Hepatic failure 2
	Postoperative (elective + emergency) 7
Chronic medical conditions	Hypertension 59
	Diabetes mellitus 40
	Coronary artery disease 40
	Chronic liver disease 28
	COPD 28
	Old CVA 13
	Peripheral vascular disease 7
	Chronic kidney disease 12
APACHE-IV score	
Range	18-119
Mean	64.14
Median	61
PCT concentration (ng/ml)	
Range	<0.05->200
Mean	9.04
Median	1.4
NTproBNP concentration (pg/ml)	
Range	45.8-90,000
Mean	13,327.76
Median	6485
Hospital mortality (%)	28
Number of hospital days	
Range	2-98
Mean	20.32
Median	10
Number of ICU days	
Range	1-98
Mean	12
Median	9
Mechanical ventilation (%)	72
Number of ventilator days	

Contd...

Table 1: Contd...

Patient characteristics	Number
Range	1-35
Mean	18.11
Median	6.5
Need for vasopressors	62

AE-COPD: Acute exacerbation of chronic obstructive pulmonary disease, CVAs: Cerebrovascular accidents, ICU: Intensive Care Unit, PCT: Procalcitonin, APACHE-IV: Acute Physiology and Chronic Health Evaluation-IV

mechanical ventilation, vasopressors), APACHE-IV score, and NTproBNP concentrations. Nonsurvivors had higher APACHE-IV, higher NTproBNP concentrations and higher need for mechanical ventilation and vasopressors ($P = 0.028$, 0.036, and 0.010, respectively). There were no statistically significant differences in terms of age, hospital stay, ICU stay, and PCT concentrations among the two groups.

Association of procalcitonin, NTproBNP, Acute Physiology, and Chronic Health Evaluation-IV with Intensive Care Unit mortality

The discriminatory ability for mortality was done with the help of ROC curve analysis for APACHE-IV, NTproBNP, and PCT. The area under the ROC curve (AUC) of APACHE-IV score and NTproBNP concentration was significantly different from 0.5 and AUC of APACHE-IV score was significantly larger than that of PCT and NTproBNP. The optimal cutoffs for APACHE-IV and NTproBNP that best predicted mortality were found to be 63.5 and 9100 pg/ml, respectively (sensitivity 64% vs. 57%; specificity 64% vs. 63%, respectively) [Figure 1].

Association of procalcitonin, NTproBNP, and Acute Physiology, and Chronic Health Evaluation-IV with morbidity

Morbidity was defined in terms of the need for mechanical ventilation and vasopressors. Patients with morbidity had longer hospital and ICU stay, higher APACHE-IV score, higher NtproBNP, and higher PCT concentrations (*P* 0.014, 0.001, 0.001, 0.013, and 0.125, respectively). But AUC for NTproBNP was significantly larger than APACHE-IV and PCT. All of these were found to be statistically significant.

Independent predictive ability for morbidity was determined with the help of ROC curve analysis of APACHE-IV, NTproBNP, and PCT. AUC of APACHE-IV, PCT, and NTproBNP were significantly different from 0.5. AUC of NTproBNP was significantly larger than that of APACHE-IV and PCT [Figure 2].

The optimal cutoffs for APACHE-IV, PCT, and NTproBNP were 63.15, 1.5 ng/ml and 4515 pg/ml, respectively

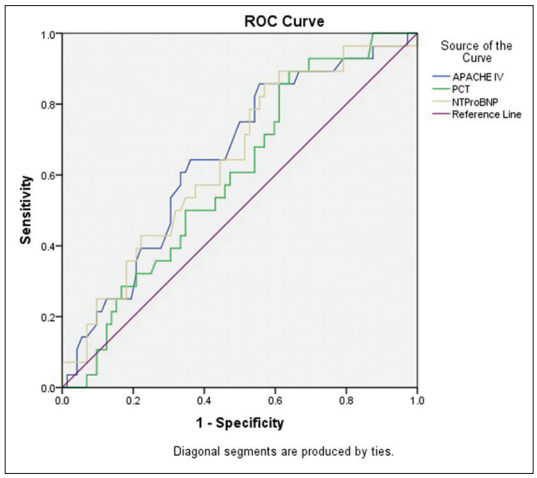

Figure 1: Mortality analysis - receiver operating characteristic curves: Acute Physiology and Chronic Health Evaluation IV-area under the curve 0.649, *P* 0.021; procalcitonin-area under the curve 0.597, *P* 0.133; NTproBNP - area under the curve 0.643, *P* 0.027

(Sensitivity 51.9%, 55.8%, and 71.4%; specificity 48.1%, 44.2%, and 28.6%, respectively).

Association of biomarkers and Acute Physiology and Chronic Health Evaluation-IV with prolonged hospital stay

Prolonged hospital stay was defined as a stay of more than 15 days. Patients with prolonged hospital stay had statistically significant more need for mechanical ventilation, vasopressors, higher APACHE-IV score, and higher PCT values (*P* 0.000, 0.023, and 0.041, respectively).

AUC of only PCT was significantly different from 0.5. AUC of PCT was significantly larger than that of APACHE-IV and NTproBNP [Figure 3].

The optimal cutoff for PCT was 0.52 ng/ml with sensitivity and specificity of 73.1% and 26.9%, respectively.

Predictors of combined morbidity and mortality

Patients who did not survive or required ventilator and/or vasopressors had statistically significant longer hospital and ICU stay, higher APACHE-IV, and higher NTproBNP values (*P* 0.018, 0.003, 0.001, and 0.017, respectively).

ROC analysis was carried out for determining the predictable power for combined morbidity and mortality. AUC of APACHE-IV, PCT, and NTproBNP concentrations were significantly different from 0.5 and AUC of NTproBNP was significantly larger than that of APACHE-IV and PCT [Figure 4].

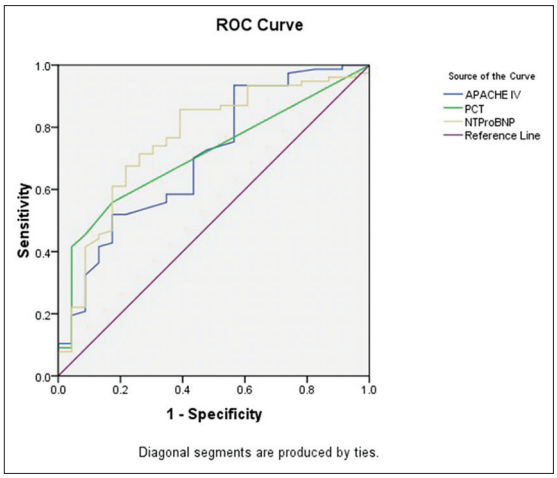

Figure 2: Morbidity analysis - receiver operating characteristic curves Acute Physiology and Chronic Health Evaluation IV-area under the curve 0.706, *P* 0.003; procalcitonin-area under the curve 0.711, *P* 0.002; NTproBNP-area under the curve 0.763, *P* 0.000

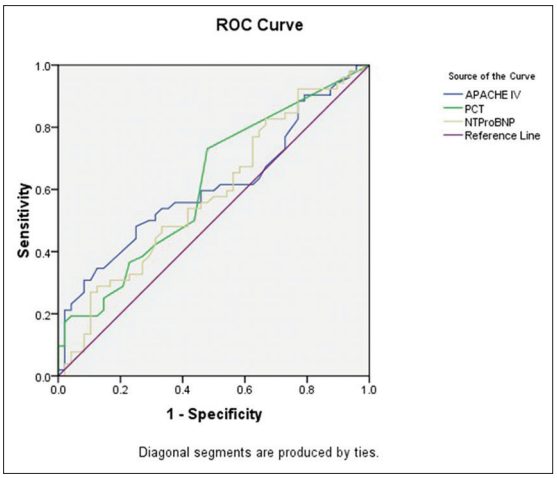

Figure 3: Hospital stay - receiver operating characteristic curves Acute Physiology and Chronic Health Evaluation-IV-area under the curve 0.608, *P* 0.063; procalcitonin-area under the curve 0.616, *P* 0.045; NTproBNP-area under the curve 0.583, *P* 0.151

The optimal cutoffs for APACHE-IV, PCT, NTproBNP were 54.5, 1.5 ng/ml and 2415 pg/ml, respectively (sensitivity 70.9%, 54.4%, and 86.1%; specificity 29.1%, 45.6%, and 13.9%, respectively).

DISCUSSION

Our study showed NTproBNP to be having a comparable predictive power for mortality and morbidity to APACE IV. PCT values showed a good correlation with morbidity (comparable to APACHE-IV) and prolonged hospital stay. However, correlation with prolonged hospital stay was not found to be statistically significant for APACHE-IV and NTproBNP.

Despite great advancements in the field of medical science, mortality from critical illness remains high. We have been relying on severity scores such as APACHE-IV and sequential organ failure assessment (SOFA) for prediction of the disease course and outcome. These are, however, fraught with a major drawback, i.e. incorporation of the worst values of the parameters in first 24 h of admission. Although still useful, these are likely to miss the set of patients who could deteriorate rapidly, and who could have benefitted from an early intervention. This has put an immense pressure on medical fraternity to identify and develop various markers which can help in the early prediction of disease severity and outcome.

Prognostic relevance for mortality

In our retrospective study, we found both APACHE-IV and NTproBNP to independently predict mortality (AUC 0.649 vs. 0.643, $P = 0.021$ vs. 027, respectively). PCT concentration, however, was not found to be predictive of mortality (AUC 0.597, $P = 0.133$). Association of NTproBNP with increased mortality was also made by Shah *et al*. in 2007. They reported NTproBNP to strongly and independently predict mortality in critically ill patients after excluding patients with decompensated heart failure and acute coronary syndrome.[4] NTproBNP has also been found to predict mortality in selective ICU population like in patients with severe sepsis.[9,10] Other authors have also reported NTproBNP's good predictability in general ICU patients.[11,12] Kotanidou *et al*. prospectively studied the role of NTproBNP in mechanically ventilated patients. They reported NTproBNP levels on ICU admission to predict renal failure and NTproBNP levels on day-3 to predict ICU mortality.[12] De Geer *et al*. found NTproBNP more than 1380 ng/l on admission to be an independent predictor of death in ICU and within 30 days in a noncardiothoracic tertiary ICU in Sweden.[13] In our study, NTproBNP more than 9100 pg/ml was found to be predictive of mortality.

PCT, on the other hand, has been found to correlate with mortality in various cohorts of critically ill patients, like after cardiopulmonary bypass;[14] in peritonitis,[15,16] and after unselected postoperative patients.[17] Similarly, Schneider *et al*. found PCT to be an independent predictor of mortality in unselected postoperative critically ill patients.[2] These findings are in contrast to our observation. However, there are few studies which did not find any correlation between PCT on admission with mortality. Two of them were performed in patients with polytrauma and abdominal surgery.[18,19] Other studies were carried out in mixed medical-surgical ICU

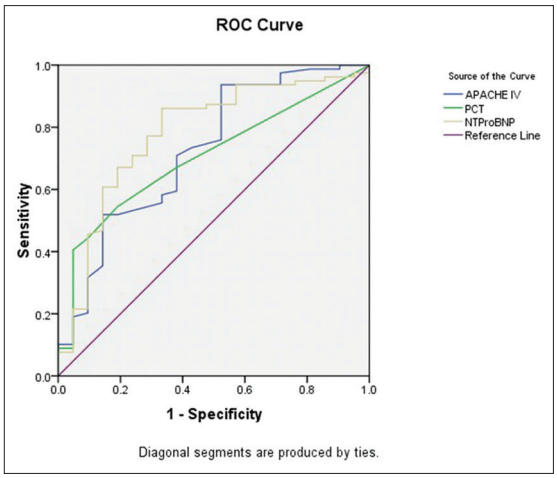

Figure 4: Combined morbidity/mortality analysis - receiver operating characteristic curves Acute Physiology and Chronic Health Evaluation IV-area under the curve 0.726, *P* 0.001; procalcitonin-area under the curve 0.704, *P* 0.004; NTproBNP-area under the curve 0.780, *P* 0.000

patients or in medical patients similar to our patient population.[20,21] These varying results may be due to different statistical methodologies used, and because of large portion of critically sick medical patients in latter studies. Although PCT has been found to have predictive power for mortality in cardiovascular medical patients,[22] the prognostic power is more reliable in surgical ICU patients. In addition, it is difficult to make direct comparisons of various studies because of the different assays employed for PCT measurement. Probably, combining PCT with NTproBNP and APACHE-IV might have improved the overall predictive power. Our study was underpowered for this purpose.

Predictive power for morbidity and hospital length of stay

In our study, we found a significant correlation between NTproBNP, APACHE-IV, PCT with morbidity in terms of the need for vasopressors and need for ventilator support. NTproBNP was found to be a better predictor of morbidity as compared to APACHE-IV and PCT (AUC 0.763, 0.706, and 0.711; *P* - value 0.000, 0.003, and 0.002, respectively). Elevated NTproBNP has been found to correlate with organ failure in a study from Greece.[12] It was also observed to be high in patients requiring ventilatory support in a couple of other studies.[5,23] However, this aspect of NTproBNP needs to be explored further. Do these observations just indicate the severity of disease is something to be ascertained?

On the other hand, association of PCT with morbidity in terms of organ failure, vasopressor or ventilatory requirement has not been studied. It has, however, been found to be indicative of severity of disease like in pancreatitis.[24,25] It has also been found to be predictive of major complications in unselected postoperative critically ill patients by Schneider *et al*.[2] In the same study, the investigators also observed PCT to be predictive of prolonged hospital stay. This is similar to the observation made by us. PCT was found to have a good predictive value for prolonged hospital stay as compared to APACHE-IV and NTproBNP, respectively (AUC 0.616, 0.608, and 0.583; *P* - value 0.045, 0.063, and 0.151, respectively). Good predictive value of PCT for postoperative complications has also been observed in trauma patients,[18,26] postcardiac surgery,[27] liver transplantation,[28] and major cancer surgery.[29] In almost all of the above-mentioned studies, authors have failed to show the superiority of PCT to established predictors of morbidity like injury severity score, SOFA score, APACHE-IV score, etc. Surprisingly, we observed almost comparable predictive power for morbidity of all the three parameters studied (NTproBNP, APACHE-IV, and PCT). However, PCT showed a clear superior predictive value for prolonged hospital length of stay. This warrants further study.

Limitations of the study

This study had several limitations. First, it was retrospective in nature. Second, it represents data from a single center. Third, a single measurement of biomarkers was taken. Results might have been different had the trending been used instead. The sample size of the study was also limited. This underpowered the study and hampered our subgroup analysis. It might have been more appropriate if trending of values had been compared to daily severity scores like SOFA. Fourth, only patients for whom both the biomarkers had been ordered at clinical discretion were included. This may have confounded the results. Moreover, the inclusion of patients with varying underlying disorders may have influenced the results. Last but not the least, banking on a single biomarker for the outcome prediction in different disease conditions may be too simplistic.

Despite the above limitations, our study has provided sufficient background for a prospective study to examine the potential of these biomarkers in early risk stratification of patients. These may prove to be useful adjuncts to time consuming and complicated predictive models normally used for ICU patients.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Yanaral TU, Idin IK, Uzmas S, Toptas M, Bican G. The prognostic value of procalcitonin and C-reactive protein in critically ill patients: A comparison with APACHE II and SOFA scores: 12AP5-2. Eur J Anaesth 2010;1068:27.
2. Schneider CP, Yilmaz Y, Kleespies A, Jauch KW, Hartl WH. Accuracy of procalcitonin for outcome prediction in unselected postoperative critically ill patients. Shock 2009;31:568-73.
3. Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, *et al.* Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: The Valsartan Heart Failure (Val-HeFT) data. Clin Chem 2006;52:1528-38.
4. Shah KB, Nolan MM, Rao K, Wang DJ, Christenson RH, Shanholtz CB, *et al.* The characteristics and prognostic importance of NT-ProBNP concentrations in critically ill patients. Am J Med 2007;120:1071-7.
5. Burke MA, Cotts WG. Interpretation of B-type natriuretic peptide in cardiac disease and other comorbid conditions. Heart Fail Rev 2007;12:23-36.
6. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.* Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.
7. Johnson CA, Levey AS, Coresh J, Levin A, Lau J, Eknoyan G. Clinical practice guidelines for chronic kidney disease in adults: Part I. Definition, disease stages, evaluation, treatment, and risk factors. Am Fam Physician 2004;70:869-76.
8. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, *et al.* An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064-89.
9. Morgenthaler NG, Struck J, Christ-Crain M, Bergmann A, Müller B. Pro-atrial natriuretic peptide is a prognostic marker in sepsis, similar to the APACHE II score: An observational study. Crit Care 2005;9:R37-45.
10. Brueckmann M, Huhle G, Lang S, Haase KK, Bertsch T, Weiss C, *et al.* Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. Circulation 2005;112:527-34.
11. Koch A, Voigt S, Sanson E, Dückers H, Horn A, Zimmermann HW, *et al.* Prognostic value of circulating amino-terminal pro-C-type natriuretic peptide in critically ill patients. Crit Care 2011;15:R45.
12. Kotanidou A, Karsaliakos P, Tzanela M, Mavrou I, Kopterides P, Papadomichelakis E, *et al.* Prognostic importance of increased plasma amino-terminal pro-brain natriuretic peptide levels in a large noncardiac, general intensive care unit population. Shock 2009;31:342-7.
13. De Geer L, Fredrikson M, Oscarsson A. Amino-terminal pro-brain natriuretic peptide as a predictor of outcome in patients admitted to intensive care. A prospective observational study. Eur J Anaesthesiol 2012;29:275-9.
14. Fritz HG, Brandes H, Bredle DL, Bitterlich A, Vollandt R, Specht M, *et al.* Post-operative hypoalbuminaemia and procalcitonin elevation for prediction of outcome in cardiopulmonary bypass surgery. Acta Anaesthesiol Scand 2003;47:1276-83.
15. Novotny A, Emmanuel K, Matevossian E, Kriner M, Ulm K, Bartels H, *et al.* Use of procalcitonin for early prediction of lethal outcome of postoperative sepsis. Am J Surg 2007;194:35-9.
16. Rau BM, Frigerio I, Büchler MW, Wegscheider K, Bassi C, Puolakkainen PA, *et al.* Evaluation of procalcitonin for predicting septic multiorgan failure and overall prognosis in secondary peritonitis: A prospective, international multicenter study. Arch Surg 2007;142:134-42.
17. Dahaba AA, Hagara B, Fall A, Rehak PH, List WF, Metzler H. Procalcitonin for early prediction of survival outcome in postoperative critically ill patients with severe sepsis. Br J Anaesth 2006;97:503-8.
18. Hensler T, Sauerland S, Lefering R, Nagelschmidt M, Bouillon B, Andermahr J, *et al.* The clinical value of procalcitonin and neopterin in predicting sepsis and organ failure after major trauma. Shock 2003;20:420-6.
19. Szakmany T, Molnar Z. Procalcitonin levels do not predict mortality following major abdominal surgery. Can J Anaesth 2003;50:1082-3.
20. Oberholzer A, Souza SM, Tschoeke SK, Oberholzer C, Abouhamze A, Pribble JP, *et al.* Plasma cytokine measurements augment prognostic scores as indicators of outcome in patients with severe sepsis. Shock 2005;23:488-93.
21. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M. Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med 2006;34:2596-602.
22. Judith K, Ritter S, Marco M. Procalcitonin as a prognostic marker in noninfected critically ill cardiovascular patients. Cardiovasc Med 2013;16:321-8.
23. Almog Y, Novack V, Megralishvili R, Kobal S, Barski L, King D, *et al.* Plasma level of N terminal pro-brain natriuretic peptide as a prognostic marker in critically ill patients. Anesth Analg 2006;102:1809-15.
24. Mándi Y, Farkas G, Takács T, Boda K, Lonovics J. Diagnostic relevance of procalcitonin, IL-6, and sICAM-1 in the prediction of infected necrosis in acute pancreatitis. Int J Pancreatol 2000;28:41-9.
25. Bülbüller N, Dogru O, Ayten R, Akbulut H, Ilhan YS, Cetinkaya Z. Procalcitonin is a predictive marker for severe acute pancreatitis. Ulus Travma Acil Cerrahi Derg 2006;12:115-20.
26. Wanner GA, Keel M, Steckholzer U, Beier W, Stocker R, Ertel W. Relationship between procalcitonin plasma levels and severity of injury, sepsis, organ failure, and mortality in injured patients. Crit Care Med 2000;28:950-7.
27. Meisner M, Rauschmayer C, Schmidt J, Feyrer R, Cesnjevar R, Bredle D, *et al.* Early increase of procalcitonin after cardiovascular surgery in patients with postoperative complications. Intensive Care Med 2002;28:1094-102.
28. Prieto B, Llorente E, González-Pinto I, Alvarez FV. Plasma procalcitonin measured by time-resolved amplified cryptate emission (TRACE) in liver transplant patients. A prognosis marker of early infectious and non-infectious postoperative complications. Clin Chem Lab Med 2008;46:660-6.
29. Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, *et al.* Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): Early markers of postoperative sepsis after major surgery. Br J Anaesth 2005;94:767-73.