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Elecsys BRAHMS PCT

cobas®

REF	Σ	SYSTEM
05056888 200	100	MODULAR ANALYTICS E170 **cobas e** 411 **cobas e** 601 **cobas e** 602

English

For use in the USA only

System information

For **cobas e** 411 analyzer: test number 510
For MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers: Application Code Number 227

Indication for use

Immunoassay for the in vitro quantitative determination of PCT (procalcitonin) in human serum and plasma (K_2-EDTA, K_3-EDTA and Li-Heparin).

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on Elecsys and **cobas e** immunoassay analyzers.

Used in conjunction with other laboratory findings and clinical assessments, Elecsys BRAHMS PCT is intended for use as follows:

- to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock,
- to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission,
- to aid in decision making on antibiotic therapy, for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD),
- to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

Warnings and precautions

- The Elecsys BRAHMS PCT is not indicated to be used as a stand-alone diagnostic assay and should be used in conjunction with clinical signs and symptoms of infection and other diagnostic evidence. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed. Changes in PCT should always be interpreted in the context of the clinical status of the patient and other laboratory results. Decisions regarding antibiotic therapy should NOT be based solely on procalcitonin concentrations.
- Biotin interference can produce either falsely high or low results. Though the risk of misclassifying a test result due to biotin interference is lower than the risks from average assay imprecision, biological variability, or other known interference, patient biotin intake and the resulting % bias should be taken into account when interpreting PCT assay values. (See Limitations - interference section below).
- Do not test samples from patients who have indicated or whose clinical status or history would indicate they are currently taking high doses of biotin (> 10 mg per day). If biotin interference is suspected, follow your established internal procedures to investigate the interference per CLIA and GLP recommendations.
- Serial draws are indicated for procalcitonin measurements. Biotin will metabolize and clear, serum levels will reduce over time.
- There is no uniformly recognized interpretation of the change in PCT concentration levels for the prediction of mortality, and overall mortality is strongly dependent on many factors, including pre-existing patient risk factors and clinical course. The need to continue ICU care at Day 4 and other covariates (e.g., age, SOFA score) are also significant predictors of 28-day cumulative mortality risk. Validation of the Elecsys BRAHMS PCT test as an aid in predicting mortality was performed in a study population with an overall 28-day mortality of 22 %.
- Certain patient characteristics, such as severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values. Increased PCT levels may be observed in severe illness such as polytrauma, burns, major surgery, prolonged or cardiogenic shock. PCT levels may not be elevated in patients infected by certain atypical pathogens, such as Chlamydia pneumoniae and Mycoplasma pneumoniae. The safety and performance of PCT-guided therapy for individuals younger than age 17 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.

Summary

Sepsis is a daily challenge in the hospital setting. Today, various therapeutic strategies are known to improve survival in patients with sepsis. Early assessment is important for determination of the appropriate treatment.

PCT is the prohormone of the hormone calcitonin, but PCT and calcitonin are distinct proteins. Calcitonin is exclusively produced by C-cells of the thyroid gland in response to hormonal stimuli, whereas PCT can be produced by several cell types and many organs in response to pro-inflammatory stimuli, in particular by bacterial products.[1]

In healthy people, plasma PCT concentrations are found to be below 0.1 ng/mL.[2] Depending on the clinical background, a PCT concentration above 0.1 ng/mL can indicate clinically relevant bacterial infection, requiring antibiotic treatment.[3] PCT levels rise rapidly (within 6-12 hours) after a bacterial infectious insult with systemic consequences. The magnitude of the increase in PCT concentration correlates with the severity of the bacterial infection.[4] At a PCT concentration > 0.5 ng/mL, a patient should be considered at risk of developing severe sepsis or septic shock.[5,6] On the other hand, the relief of the septic infection is accompanied by a decrease in the PCT concentration which returns to normal with a half-life of 24 hours,[7,8] i.e., the continuous decline of PCT is indicative of effective source control measures and has been implicated in the safe de-escalation of antibiotic therapy.[9,10]

By evaluating PCT concentrations, the physician may use the findings to aid in the risk assessment of critically ill patients for progression to severe sepsis and septic shock. In addition, the change of PCT levels over time offers information about the risk of mortality after diagnosis of severe sepsis or septic shock.

Early after multiple traumas, major surgery, severe burns, or in neonates, PCT levels can be elevated independently of an infectious process, but the return to baseline is usually rapid. Viral infections, bacterial colonization, localized infections, allergic disorders, autoimmune diseases, and transplant rejection do not usually induce a significant PCT response (values < 0.5 ng/mL). Therefore, PCT is an important marker enabling specific differentiation between a bacterial infection and other causes of inflammatory reactions.[3]

The results of the Elecsys BRAHMS PCT assay on the Elecsys and **cobas e** analyzers should be evaluated in the context of all laboratory findings and the total clinical status of the patient. In cases where laboratory results do not agree with the clinical picture or history, additional tests should be performed.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: Antigen in the sample (30 µL), a biotinylated monoclonal PCT-specific antibody, and a monoclonal PCT-specific antibody labeled with a ruthenium complex[a)] react to form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.

- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined via a calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode or e-barcode.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The reagent rackpack (M, R1, R2) is labeled as PCT.

M Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL: Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 Anti-PCT-Ab~biotin (gray cap), 1 bottle, 9 mL: Biotinylated monoclonal anti-PCT antibody (mouse) 2.0 µg/mL; phosphate buffer 95 mmol/L, pH 7.5; preservative.

R2 Anti-PCT-Ab~$Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 mL: Monoclonal anti-PCT antibody (mouse) labeled with ruthenium complex 5.6 µg/mL; phosphate buffer 95 mmol/L, pH 7.5; preservative.

PCT Cal1 PCT calibrator 1 (white cap), 1 bottle (lyophilized) for 4 mL: PCT (recombinant) approximately 0.10 ng/mL in a human serum matrix; preservative.

PCT Cal2 PCT calibrator 2 (black cap), 1 bottle (lyophilized) for 4 mL: PCT (recombinant) approximately 54 ng/mL in a human serum matrix; preservative.

PC PCT1 PreciControl PCT 1 (beige cap), 2 bottles (lyophilized) each for 4 mL: PCT (recombinant) approximately 0.50 ng/mL in a human serum matrix; preservative.

PC PCT2 PreciControl PCT 2 (brown cap), 2 bottles (lyophilized) each for 4 mL: PCT (recombinant) approximately 10 ng/mL in a human serum matrix; preservative.

Calibrators: The exact lot-specific calibrator values are encoded in the barcoded labels of the test-specific reagent.

Controls: The exact lot-specific target values and ranges are encoded in the barcodes as well as printed on the enclosed (or electronically available) value sheet.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

2-methyl-2H-isothiazol-3-one hydrochloride

EUH 208 May produce an allergic reaction.

Product safety labeling follows EU GHS guidance.

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

However, as no testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[11,12]

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

The reagents in the kit (M, R1 and R2) are ready-for-use and are supplied in bottles compatible with the system.

Calibrators and controls

Carefully dissolve the contents of one bottle by adding exactly 4 mL of distilled or deionized water and allow to stand closed for 15 minutes to reconstitute. Mix carefully, avoiding foam formation. Transfer the reconstituted calibrators/controls into empty labeled snap-cap bottles.

Unless the entire volume is necessary for calibration and quality control on the analyzer, transfer aliquots of the freshly reconstituted calibrators and controls into empty snap-cap bottles (CalSet Vials/ControlSet Vials). Attach the supplied labels to these additional bottles. Store the aliquots at -20 ± 5 °C for later use. Perform **only one** calibration or control procedure per aliquot.

Note: Do not combine bottles from different lots. Use only control bottles out of one lot with each other.

All information required for correct operation is read in from the respective reagent barcodes.

Please note: Both the vial labels, and the additional labels (if available) contain 2 different barcodes. The barcode between the yellow markers is for **cobas** 8000 systems only. If using a **cobas** 8000 system, please turn the vial cap 180° into the correct position so the barcode can be read by the system. Place the vial on the instrument as usual.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the Elecsys reagent kit **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the reagent rackpack	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	12 weeks
on the analyzers	4 weeks

Stability of the calibrators and controls	
lyophilized calibrators/controls	up to the stated expiration date
reconstituted calibrators/controls on the analyzers	2 hours (use only once)
reconstituted calibrators/controls at -20 ± 5 °C	3 months (freeze only once)

Store the calibrators and controls **upright** in order to prevent the solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes or tubes containing separating gel.

Li-heparin, K_2-EDTA and K_3-EDTA plasma, as well as Li-heparin plasma tubes containing separating gel.

Stable for 24 hours at 15-25 °C, 48 hours at 2-8 °C, 3 months at -20 ± 5 °C. Freeze and thaw only once.

Centrifuge samples containing precipitates before performing the assay.

Do not use samples and controls stabilized with azide.

Ensure the samples, calibrators and controls are at 15-25 °C prior to measurement.

Due to possible evaporation effects, samples, calibrators and controls on the analyzers should be analyzed/measured within 2 hours.

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary

tubes (sample collection systems), follow the instructions of the tube manufacturer.

The claims, including those pertaining to sample stability made in the labeling of the cleared/approved reagents of Roche Diagnostics are part of the clearance of the overall IVD test system (assay). Sample stability was tested only for the temperatures/time frame as claimed by the manufacturer under the conditions claimed in the method sheet. It is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for its laboratory.

Materials provided

See "Reagents – working solutions" section for reagents.

- 2 barcode cards
- Control barcode sheet
- 2 x 8 bottle labels (calibrators)
- 2 x 14 bottle labels (controls)
- 6 empty labeled snap-cap bottles

Materials required (but not provided)

- REF 11776576322, CalSet Vials, 2 x 56 empty snap-cap bottles
- REF 03142949122, ControlSet Vials, 2 x 56 empty snap-cap bottles
- General laboratory equipment
- distilled or deionized water
- MODULAR ANALYTICS E170 or **cobas e** analyzer

Accessories for **cobas e** 411 analyzer:

- REF 11662988122, ProCell, 6 x 380 mL system buffer
- REF 11662970122, CleanCell, 6 x 380 mL measuring cell cleaning solution
- REF 11930346122, Elecsys SysWash, 1 x 500 mL washwater additive
- REF 11933159001, Adapter for SysClean
- REF 11706802001, AssayCup, 60 x 60 reaction cups
- REF 11706799001, AssayTip, 30 x 120 pipette tips
- REF 11800507001, Clean-Liner

Accessories for MODULAR ANALYTICS E170, **cobas e** 601 and **cobas e** 602 analyzers:

- REF 04880340190, ProCell M, 2 x 2 L system buffer
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 03023141001, PC/CC-Cups, 12 cups to prewarm ProCell M and CleanCell M before use
- REF 03005712190, ProbeWash M, 12 x 70 mL cleaning solution for run finalization and rinsing during reagent change
- REF 12102137001, AssayTip/AssayCup, 48 magazines x 84 reaction cups or pipette tips, waste bags
- REF 03023150001, WasteLiner, waste bags
- REF 03027651001, SysClean Adapter M

Accessories for all analyzers:

- REF 11298500160, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use. Read in the test-specific parameters via the reagent barcode. If in exceptional cases the barcode cannot be read, enter the 15-digit sequence of numbers (except for the **cobas e** 602 analyzer).

Bring the cooled reagents to approximately 20 °C and place on the reagent disk (20 °C) of the analyzer. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the bottles.

Place the reconstituted calibrators (in the system-compatible bottles with barcoded labels) in the sample zone.

All the information necessary for calibrating the assay is automatically read into the analyzer.

After calibration has been performed, discard the calibrators.

Analyze the controls PC PCT1 and PC PCT2. The information on the barcoded label of the control serum bottle is read in automatically. After the control procedure has been performed, discard the controls.

Calibration

Traceability: This method has been standardized against the BRAHMS PCT LIA assay.

Every Elecsys reagent set has a barcoded label containing specific information for calibration of the particular reagent lot. The predefined master curve is adapted to the analyzer using PCT Cal1 and PCT Cal2.

Note: Calibrator sequence on all systems: Always measure PCT Cal2 before PCT Cal1.

Calibration frequency: Calibration must be performed once per reagent lot using PCT Cal1, PCT Cal2 and fresh reagent (i.e. not more than 24 hours since the reagent kit was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 8 weeks when using the same reagent lot
- after 7 days (when using the same reagent kit on the analyzer)
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use PC PCT1 and PC PCT2.

In addition, other suitable control material can be used.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per reagent kit, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Note: When using two reagent kits with different lots in the same run, the controls will be measured with both reagent lots. Use only control values measured with the corresponding lots.

Calculation

The analyzer automatically calculates the analyte concentration of each sample in ng/mL.

High-dose hook effect

There is no high-dose hook effect at PCT concentrations up to 1000 ng/mL.

Limitations - interference

The assay is unaffected by icterus (bilirubin < 428 µmol/L or < 25 mg/dL), hemolysis (Hb < 0.559 mmol/L or < 0.900 g/dL) and lipemia (Intralipid < 1500 mg/dL). Recovery was within ± 15 % of the initial value.

Biotin interference**

% Bias for samples containing various concentrations of biotin					
Samples PCT concentrations (ng/mL)	Biotin concentration (ng/mL)				
	9.6	20.4	30.0	39.6	80.4
0.04	2.3	2.8	0.2	-17.0	*
0.10	4.5	-2.8	-6.6	-13.2	-26.8
0.13	0.5	-2.8	-3.1	-4.8	-25.1
0.20	1.5	0.3	-8.6	-11.5	-38.4
0.48	0.9	0.5	-0.03	-0.5	-9.1
1.96	3.9	3.6	1.4	0.5	-8.0

% Bias for samples containing various concentrations of biotin					
Samples PCT concentrations (ng/mL)	Biotin concentration (ng/mL)				
	99.6	150	300	600	1200
0.04	-65.7	*	*	*	*
0.10	-55.2	-83.3	*	*	*
0.13	-45.8	-68.4	*	*	*
0.20	-50.9	-75.8	*	*	*
0.48	-15.5	-26.8	-60.5	-97.7	*
1.96	-12.7	-24.1	-60.5	-92.0	-97.5

* = value below measurable range

** Specimens with biotin concentrations up to 30 ng/mL demonstrated ≤ 13 % bias in results. Biotin concentrations greater than 30 ng/mL can lead to higher negative bias for PCT results. The recommended daily intake for biotin is 30 µg. Higher doses of biotin (> 10 mg per day) may be taken as a dietary supplement aimed at reducing hair loss or improving nail or skin condition.[13]

Some pharmacokinetic studies have shown that serum concentrations of biotin can reach 355 ng/mL for subjects taking supplements containing at least 20 mg of biotin[14] or 1160 ng/mL for subjects taking doses of biotin up to 300 mg.[13] These studies were performed in healthy subjects, and some patients may be taking supplements with biotin at levels greater than 20 mg per day. Clearance of biotin could be different in patients tested with this device, which may lead to higher than expected concentrations of biotin in serum.

Other interferent testing:

- No interference was observed from rheumatoid factors up to a concentration of 1500 IU/mL.
- Human Anti-Mouse Antibody (HAMA) interference testing was completed with three PCT analyte concentrations using a high HAMA human serum pool. No interference was detected.
- Samples from patients routinely exposed to animals or animal serum products may contain heterophilic antibodies causing an atypical result. This assay has been formulated to mitigate the risk of this type of interference. However, potential interactions between rare sera and test components can occur.
- In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.
- In vitro tests were performed on 38 commonly used pharmaceuticals. No interference with the assay was found. The specific drugs were tested with concentrations shown in the table below.

  Recovery was within ± 10 % of the reference value.

Active agent	Concentration mg/L
Acetylcysteine	150
Ampicillin	1000
Ascorbic acid	300
Ca-Dobesilate	200
Cyclosporine	5
Cefoxitin	2500
Heparin	8000 U
Levodopa	20
Methyldopa	20
Metronidazole	200
Phenylbutazone	400
Doxycycline	50
Acetylsalicylic acid	1000
Rifampicin	60
Acetaminophen	200
Ibuprofen	500
Theophylline	100
Imipenem	1180
Cefotaxin	900
Vancomycin	3500
Dopamine	130
Noradrenaline	2
Dobutamine	11.2
Furosemide	200000
Calcitonin Eel	30
Calcitonin Salmon	30
Fentanyl	10
Cromolyn	24
Alcohol	4000
Azithromycin	11.5
Cetirizine HCl	3.6
Dextromethorphan	1.4
Levofloxacin	17.5
Loratadine	0.3
Nicotine	1
Oxymetazoline HCl	0.09
Phenylephrine	0.18
Tiotropium	0.0216

Limitations

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Increased PCT levels may not always be related to systemic infection.[4,15,16,17] These include, but are not limited to:

Patients experiencing major trauma and/or recent surgical procedure including extracorporeal circulation or burns.

Patients undergoing treatment with OKT3 antibodies, OK-432, interleukins, TNF-alpha and other drugs that stimulate the release of pro-inflammatory cytokines or result in anaphylaxis.

Patients diagnosed with active medullary C-cell carcinoma, small cell lung carcinoma, or bronchial carcinoid.

Patients with acute or chronic viral hepatitis and/or decompensated severe liver cirrhosis (Child-Pugh Class C).

Patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, or after resuscitation from cardiac arrest.

Patients receiving peritoneal dialysis or hemodialysis treatment.

Patients with biliary pancreatitis, chemical pneumonitis or heat stroke.

Patients with invasive fungal infections (e.g., candidiasis, aspergillosis) or acute attacks of plasmodium falciparum malaria.

Neonates during the first 2 days of life.

The results of the Elecsys BRAHMS PCT assay should be evaluated in the context of all laboratory findings and the total clinical status of the patient. In cases where laboratory results do not agree with the clinical picture or history, additional tests should be performed.

Limits and ranges

Measuring range

0.02-100 ng/mL (defined by the Limit of Detection and the maximum of the master curve). Values below the Limit of Detection are reported as < 0.02 ng/mL. Values above the measuring range are reported as > 100 ng/mL.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation:

Limit of Blank = 0.015 ng/mL
Limit of Detection = 0.02 ng/mL
Limit of Quantitation = 0.060 ng/mL

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples. The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is determined as the lowest concentration of analyte that can be quantified with a total allowable error of 20 %.

Expected value ng/mL	Elecsys BRAHMS PCT		
	% CV	% BIAS	% TE
2.00	2.37	1.94	5.85
0.50	2.40	2.17	6.13
0.30	3.00	2.50	7.44
0.25	3.41	2.70	8.32
0.15	5.38	3.7	12.57
0.10	8.11	5.35	18.73
0.05	16.65	12.45	39.92

Dilution

Samples with PCT concentrations above the measuring range can be diluted manually with PCT-negative human serum or plasma. The recommended dilution is 1:4. The concentration of the diluted sample must be ≥ 20 ng/mL.

After manual dilution, multiply the result by the dilution factor.

Interpretation of the results

This assay is intended for use to determine the change of PCT over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU, or when obtained in the emergency department or other medical wards prior to ICU admission.

SIRS (Systemic Inflammatory Response Syndrome), sepsis, severe sepsis, and septic shock were categorized according to the criteria of the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine.[18]

PCT should always be interpreted in the clinical context of the patient. Therefore, clinicians should use the PCT results in conjunction with other laboratory findings and clinical signs of the patient.

Data support the following interpretative risk assessment criteria:[19,20]

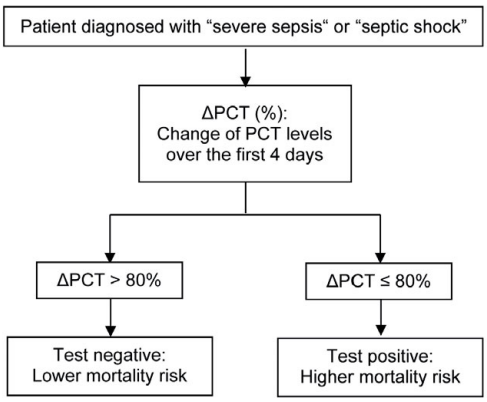
PCT > 2 ng/mL
A PCT level above 2.0 ng/mL on the first day of ICU admission is associated with a high risk for progression to severe sepsis and/or septic shock.

PCT < 0.5 ng/mL
A PCT level below 0.5 ng/mL on the first day of ICU admission is associated with a low risk for progression to severe sepsis and/or septic shock.

Note: Concentrations < 0.5 ng/mL do not exclude an infection, on account of localized infections (without systemic signs) which can be associated with such low concentrations, or a systemic infection in its initial stages (< 6 hours). Furthermore, increased procalcitonin can occur without infection. PCT concentrations between 0.5 and 2.0 ng/mL should be interpreted taking into account the patient's history. It is recommended to retest PCT within 6-24 hours if any concentrations < 2 ng/mL are obtained.

The change of PCT concentration over time provides prognostic information about the risk of mortality[21] within 28 days for patients diagnosed with severe sepsis or septic shock coming from the emergency department, ICU, other medical wards, or directly from outside the hospital. Data support the use of PCT determinations from the day severe sepsis or septic shock is first diagnosed (Day 0) or the day thereafter (Day 1) and the fourth day after diagnosis (Day 4) for the classification of patients into higher and lower risk for mortality within 28 days according to the workflow below:

$$\Delta PCT = \frac{PCT_{\text{Day0 (or Day1)}} - PCT_{Day4}}{PCT_{Day0\ (or\ Day1)}} \times 100\%$$



ΔPCT ≤ 80 %
A decrease of PCT levels below or equal to 80 % defines a positive ΔPCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

ΔPCT > 80 %
A decrease of PCT levels of more than 80 % defines a negative ΔPCT result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

If Day 0 result is not available, Day 1 result may be used.
If more than one PCT value is available on Day 0 (or Day 1), enter the highest value.
If more than one PCT value is available on Day 4, enter the most recent value.

For convenience, one can use the Change in Procalcitonin Calculator to determine ΔPCT results from the absolute PCT concentrations of a patient obtained on the day severe sepsis or septic shock was first diagnosed (or 24 hours later) and on Day 4.

Go to www.BRAHMS-PCT-Calculator.com.
Note: By using this website tool, you are visiting a 3rd party website. Roche is not responsible for the content of this website. The upper end of the measuring range for the Elecsys BRAHMS PCT assay is 400 ng/mL when using a 1:4 dilution.

Elecsys BRAHMS PCT

cobas®

Decision making on antibiotic therapy for patients with suspected or confirmed LRTI

Initiation:

PCT result	< 0.10 ng/mL	0.10-0.25 ng/mL	0.26-0.50 ng/mL	> 0.50 ng/mL
Interpretation	Antibiotic therapy strongly discouraged. Indicates absence of bacterial infection.	Antibiotic therapy discouraged. Bacterial infection unlikely.	Antibiotic therapy encouraged. Bacterial infection possible.	Antibiotic therapy strongly encouraged. Suggestive of presence of bacterial infection.
Follow-up	Antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted. If antibiotics are withheld, reassess if symptoms persist/worsen and/or repeat PCT measurement within 6-24 hours.		In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1-2 days,[22] based upon physician discretion taking into account patient's evolution and progress. Antibiotic therapy may be adjusted using the discontinuation table below:	

Discontinuation:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.25 ng/mL or if the ΔPCT > 80 %.

- PCT_{Peak}: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\triangle PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \times 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as apparent progression on chest x-ray or ongoing/increasing toxicity.

If clinical picture has not improved, and PCT remains high, re-evaluate and consider treatment failure or other causes.

Decision making on antibiotic discontinuation for suspected or confirmed septic patients

In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1-2 days,[22] based upon physician discretion taking into account the patients' evolution and progress. Antibiotic therapy may be adjusted using the discontinuation table below:

Antibiotic therapy may be discontinued if the $PCT_{Current}$ is ≤ 0.50 ng/mL or if the ΔPCT > 80 %

- PCT_{Peak}: Highest observed PCT concentration.
- $PCT_{Current}$: Most recent PCT concentration.
- ΔPCT: Calculate by using the following equation:

$$\triangle PCT = \frac{PCT_{Peak} \square - PCT_{Current} \square}{PCT_{Peak} \square} \times 100\%$$

Antibiotic therapy may be continued based upon other clinical findings, such as failure to control a local infection, or ongoing physiologic instability.

If clinical picture has not improved, and PCT remains high, re-evaluate and consider treatment failure or other causes.

Recommendations for laboratory reports

It is suggested to report the numerical PCT values (individual or paired). For paired PCT values the report should also indicate if the ΔPCT(%) was ≤ 80 % or > 80 %. The laboratory report should include a reference or a link to the Elecsys BRAHMS PCT assay package insert for a guided interpretation of the test results.
www.BRAHMS-PCT-Calculator.com
Alternatively, the laboratory report may provide such interpretative criteria directly (as found on the website above) together with the absolute PCT concentrations and the "Change in Procalcitonin Result".

Clinical performance

The Elecsys BRAHMS PCT assay was evaluated for the prediction of cumulative 28-day all-cause mortality in a prospective clinical trial[23] study of 858 adult patients diagnosed with severe sepsis or septic shock admitted to ICU care in which PCT levels were measured on Days 0, 1, and 4 across 13 investigational sites in the US. The per protocol analysis population (598 subjects) was comprised of 44 % female and 56 % male patients with a mean age of 64 years. About half of the patients had severe sepsis (51 %) versus septic shock (49 %). Infections were mainly community acquired (91 %).

The binary test result (ΔPCT > 80 % or ≤ 80 %) was significantly associated with 28-day cumulative mortality (vital status on day 28) (Two-sided Fisher's Exact Test p-value = 0.002). Adjusted for ICU vs. non-ICU patient subgroups (based on hospital location at Day 4 after initial diagnosis), the association remained significant (Cochran-Mantel-Haenszel Test p-value = 0.020). In each binary ΔPCT subgroup, the 28-day cumulative mortality rate was stratified by need to continue ICU care on Day 4 and/or the selection of Day 0 vs. Day 1 as the baseline measurement day for the ΔPCT calculation. The data are as follows:

Prediction performances of binary ΔPCT stratified by ICU care on Day 4

28-Day mortality risk stratified by patient location on Day 4: ΔPCT > 80 % = Test Negative; ΔPCT ≤ 80 % = Test Positive per-protocol population

Day 4 patient location	Measurement interval	28-Day mortality risk (%)		Prognostic accuracy[b)]	
		ΔPCT > 80 %	ΔPCT ≤ 80 %	Sensitivity	Specificity
ICU	ΔPCT Day 0-4	22.1 (13.3-31.0)	29.6 (22.9-36.4)	73.4 (62.9-83.8)	35.0 (28.2-41.8)
	ΔPCT Day 1-4	21.5 (13.0-29.9)	30.4 (23.4-37.3)	71.6 (60.8-82.3)	38.7 (31.7-45.7)
Non-ICU	ΔPCT Day 0-4	5.6 (1.8-9.4)	11.0 (6.6-15.5)	72.3 (55.9-88.6)	44.4 (38.4-50.3)
	ΔPCT Day 1-4	7.1 (2.8-11.3)	9.9 (5.7-14.2)	65.4 (48.0-82.7)	43.3 (37.3-49.2)

b) Prognostic accuracy refers to how accurate the ΔPCT (> 80 % vs. ≤ 80 %) can predict mortality risk using 28-day mortality as the clinical reference.

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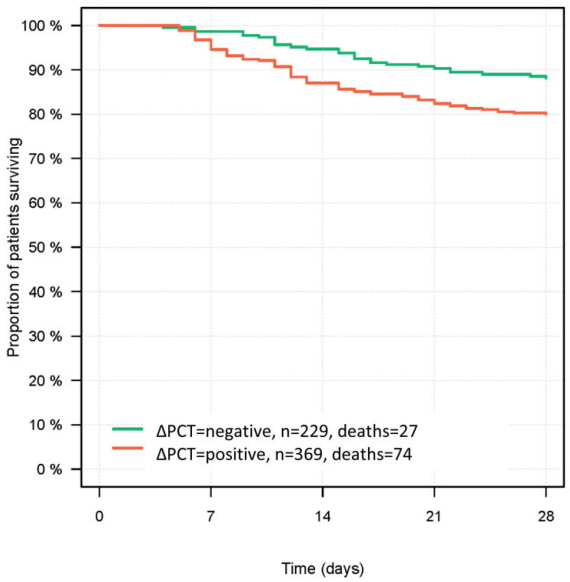
Kaplan-Meier survival curves show that patients with a positive ΔPCT result (≤ 80 %) had a clearly lower survival probability from study Day 4 till the end of follow-up time compared to ΔPCT-negative (> 80 %) patients.



Additional stratification of patients based on absolute initial PCT levels (> or ≤ 2.0 ng/mL) at Day 0 (or Day 1) revealed subgroups with particularly reduced or elevated mortality risk considering their hospital disposition on Day 4. Mortality rates and prognostic performance are given for the following subgroups in the table below:

1. Patients with PCT ≤ 2.0 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4.
2. Patients with PCT > 2.0 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4.
3. Patients with PCT ≤ 2.0 ng/mL at Day 0 (or Day 1) without ICU care on Day 4.
4. Patients with PCT > 2.0 ng/mL at Day 0 (or Day 1) without ICU care on Day 4.

28-Day mortality risk stratified by patient location on Day 4, absolute PCT value on Day 0: ΔPCT > 80 % = Test Negative; ΔPCT ≤ 80 % = Test Positive

Per-Protocol Population: ΔPCT 0-4 stratified PCT at Day 0

Day 4 patient location	PCT at Day 0	28-Day mortality risk (%)		Prognostic accuracy[c]	
		ΔPCT Day 0-4 > 80 %	ΔPCT Day 0-4 ≤ 80 %	Sensitivity (%)	Specificity (%)
ICU	≤ 2.0 ng/mL	10.4 (0.0-29.7)	24.9 (15.2-34.6)	94.9 (85.2-100)	13.3 (4.9-21.8)
	> 2.0 ng/mL	23.6 (14.0-33.2)	33.2 (24.0-42.4)	65.1 (51.8-78.3)	46.3 (37.5-55.0)
Non-ICU	≤ 2.0 ng/mL	5.6 (0.0-16.3)	8.3 (3.6-12.9)	91.7 (76.0-100)	12.3 (6.2-18.4)
	> 2.0 ng/mL	5.6 (1.6-9.7)	17.5 (7.5-27.5)	58.6 (35.1-82.1)	71.4 (64.1-78.8)

c) Prognostic accuracy refers to how accurate the ΔPCT (> 80 % vs. ≤ 80 %) can predict mortality risk.

28-Day mortality risk stratified by patient location on Day 4, absolute PCT value on Day 1: ΔPCT > 80 % = Test Negative; ΔPCT ≤ 80 % = Test Positive

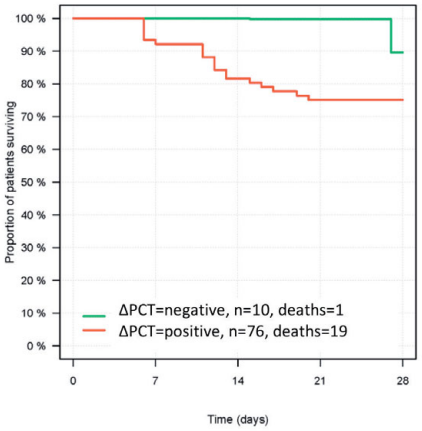
Per-Protocol Population: ΔPCT 1-4 stratified PCT at Day 1

Day 4 patient location	PCT at Day 1	28-Day mortality risk (%)		Prognostic accuracy[c]	
		ΔPCT Day 1-4 > 80 %	ΔPCT Day 1-4 ≤ 80 %	Sensitivity (%)	Specificity (%)
ICU	≤ 2.0 ng/mL	11.8 (0.0-33.6)	25.5 (15.4-35.6)	94.7 (84.6-100.0)	12.7 (3.8-21.7)
	> 2.0 ng/mL	22.5 (13.5-31.5)	34.0 (24.4-43.5)	62.9 (49.4-76.5)	51.3 (42.4-59.7)
Non-ICU	≤ 2.0 ng/mL	0.0 (0.0-17.6)[d]	7.5 (3.0-12.0)	100.0 (69.2-100.0)[d]	13.4 (7.3-19.5)
	> 2.0 ng/mL	8.2 (3.3-13.1)	15.3 (6.0-24.7)	47.2 (24.6-69.7)	69.4 (61.6-77.2)

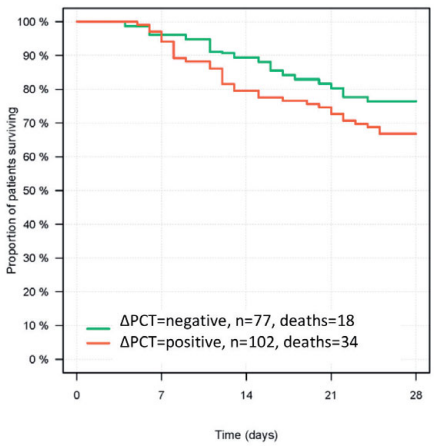
d) Normality approximation of within-imputation variance not valid, therefore the estimate corresponds to within-imputation variation based on exact confidence intervals [Clopper & Pearson, 1934]

Kaplan-Meier Plots are depicted below to illustrate the time-to-event structure in the extended patient subgroups according to hospital location on Day 4 and initial PCT level.

Survival until Day 28, PCT ≤ 2.0 ng/mL at Day 0, ICU Day 4 (n=86)



Survival until Day 28, PCT > 2.0 ng/mL at Day 0, ICU Day 4 (n=179)



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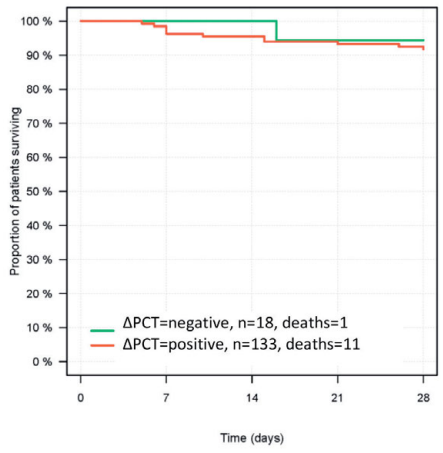
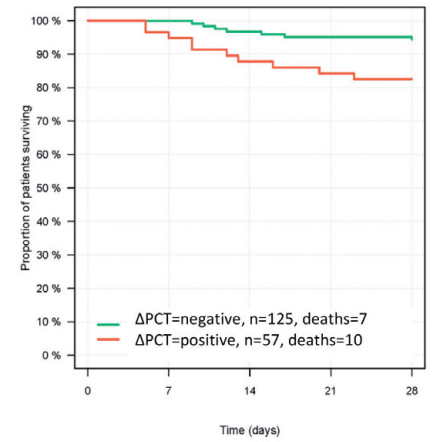
Survival until Day 28, PCT ≤ 2.0 ng/mL at Day 0, non-ICU Day 4 (n=151)



Survival until Day 28, PCT > 2.0 ng/mL at Day 0, non-ICU Day 4 (n=182)



Time-to-event analysis reveals that patients in the ICU or with an initial PCT value > 2.0 ng/mL had a lower survival probability from study Day 4 until the end of follow-up time (28 days) when the ΔPCT test result was positive compared to ΔPCT-negative patients as illustrated by the Kaplan-Meier curves above (patient subgroups according to hospital location on Day 4 and initial PCT level).

A generally lower mortality rate was observed in the non-ICU subgroup. The mortality rates for ΔPCT > 80 % vs. ΔPCT ≤ 80 % patient subgroups were:

Patients with PCT ≤ 2.0 ng/mL at Day 0 receiving ICU care on Day 4	10.4 % vs. 24.9 %
Patients with PCT > 2.0 ng/mL at Day 0 receiving ICU care on Day 4	23.6 % vs. 33.2 %
Patients with PCT ≤ 2.0 ng/mL at Day 0 without ICU care on Day 4	5.6 % vs. 8.3 %
Patients with PCT > 2.0 ng/mL at Day 0 without ICU care on Day 4	5.6 % vs. 17.5 %

Based on relative mortality ratios a decrease by more than 80 % from Day 0 (or Day 1) to Day 4 constitutes a lower risk for mortality within 28 days compared to smaller declines in each subgroup. For the prediction of absolute mortality risks ICU disposition at Day 4 and initial PCT concentrations should be considered:

1. An initial PCT level ≤ 2.0 ng/mL on Day 0 followed by a PCT decline of more than 80 % until Day 4 indicates an almost 2-fold lower mortality (10.4 %) for patients with severe sepsis or septic shock who are still in the ICU by Day 4 compared to those patients with an initial PCT level > 2.0 ng/mL (23.6 %). Regardless of the initial PCT level, patients in the ICU on Day 4 that do not decline by more than 80 % in PCT plasma concentration from Day 0 to Day 4 have an even higher mortality risk of 24.9-33.2 %.
2. An initial PCT level > 2.0 ng/mL that does not decline by more than 80 % until Day 4 signals that such patients remain at high mortality risk (17.5 %) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 5.6 to 8.3 % for patients discharged from the ICU by Day 4.

In conclusion, hazard ratios for binary ΔPCT for both subgroups enrolled show an increase in mortality with ΔPCT. The mortality risk stratification using ΔPCT is valid when calculated from the day severe sepsis or septic shock is first diagnosed (Day 0) or the day thereafter (Day 1) and compared to the fourth day (Day 4) after diagnosis. The ΔPCT at Day 4 combined with the patient's clinical course provides important information for the 28-day all-cause mortality risk prediction after a diagnosis of severe sepsis or septic shock.

The prognostic value of ΔPCT was quantified by pooled p-values of Wald statistics (Rubin's rule). The hazard ratio of binary ΔPCT at Day 4 in the univariate model is 1.80 (p = 0.011) for patients of the Per-Protocol population. That means **the risk of death is increased 1.8-fold if an individual has a positive test result for ΔPCT.**

As a comparison, the table below lists the univariate hazard ratios for other clinical factors evaluated as separate predictors of mortality in the per protocol study population.

Univariate hazard ratios for 28-day all-cause mortality of ΔPCT and clinical covariates

Factor	Comparison	Hazard ratio	p-Value
ΔPCT Day 0-4	≤ 80 % vs. > 80 %	1.80 (1.15-2.82)	0.011
ΔPCT Day 1-4	≤ 80 % vs. > 80 %	1.61 (1.04-2.49)	0.034
APACHE	Difference of 5 units	1.36 (1.22-1.53)	< 0.001
Max SOFA	Difference of 3 units	1.73 (1.50-2.00)	< 0.001
Antibiotic adequacy	No vs. yes	1.59 (1.00-2.53)	0.051
Sepsis severity	Septic shock vs. severe sepsis	1.19 (0.80-1.76)	0.386
Biologic infection type	Gram pos vs. gram neg	0.83 (0.48-1.45)	0.522
Biologic infection type	Other vs. gram neg	0.99 (0.63-1.54)	0.960
Biologic infection type	Fungal vs. gram neg	2.44 (0.87-6.84)	0.090
Clinical infection type	Nosocomial vs. community	0.76 (0.35-1.64)	0.481
Positive blood culture	Yes vs. no	1.05 (0.69-1.58)	0.834
Baseline PCT	> 2 ng/mL vs. ≤ 2 ng/mL	1.43 (0.94-2.17)	0.095
Age	Difference of 5 years	1.16 (1.08-1.24)	< 0.001
Gender	Male vs. female	0.95 (0.64-1.40)	0.782

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Univariate hazard ratios for 28-day all-cause mortality of ΔPCT and clinical covariates			
Factor	**Comparison**	**Hazard ratio**	**p-Value**
ICU care on Day 4	Yes vs. no	3.45 (2.24-5.31)	< 0.001

ΔPCT from Day 0 (or Day 1) to Day 4 remains a prognostic parameter for the risk of cumulative 28-day mortality in patients diagnosed with severe sepsis or septic shock even when hazard ratios are adjusted for other mortality predictors in multivariate models. The relative mortality risk estimates for ΔPCT and selected predictors are given below with 95 % confidence intervals. For continuous predictors, the hazard ratio (HR) was calculated for one standard deviation (SD) change in the predictor. For binary predictors, the risk estimate compares the hazards for the two binary results.

Hazard ratios for ΔPCT were calculated for each group as univariate and when applying certain covariates and are tabulated below.

Hazard ratios for ΔPCT per group	
Hazard ratio for ΔPCT ≤ 80 %	**Per-protocol**
ΔPCT Day 0-4 (univariate)	**1.80** [1.15-2.82]; p=0.0106
ΔPCT Day 0-4 with binary APACHE + covariates[e)]	**1.94** [1.14-3.31]; p=0.0140
ΔPCT Day 0-4 with numeric APACHE + covariates[e)]	**1.72** [1.00-2.95]; p=0.0487
ΔPCT Day 0-4 with binary SOFA + covariates[e)]	**1.76** [1.05-2.96]; p=0.0320
ΔPCT Day 0-4 with numeric SOFA + covariates[e)]	**1.46** [0.86-2.48]; p=0.1595
ΔPCT Day 1-4 (univariate)	**1.61** [1.04-2.49]; p=0.0345
ΔPCT Day 1-4 with binary APACHE + covariates[e)]	**1.68** [1.03-2.76]; p=0.0392
ΔPCT Day 1-4 with numeric APACHE + covariates[e)]	**1.61** [0.98-2.65]; p=0.0625
ΔPCT Day 1-4 with binary SOFA + covariates[e)]	**1.64** [1.00-2.69]; p=0.0483
ΔPCT Day 1-4 with numeric SOFA + covariates[e)]	**1.47** [0.89-2.42]; p=0.1300

e) Antibiotic adequacy, Sepsis severity, ICU Care on Day 4, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Age, Gender

Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models			
Model		**Hazard ratio (95 % confidence interval)**	
		Binary predictors[f)]	
ΔPCT interval	**Score + Covariates[g)]**	**ΔPCT (≤ 80 % vs > 80 %)**	**Day 4 patient location (ICU vs. no ICU)**
Day 0 until Day 4	APACHE	1.72 (1.00-2.95)	2.61 (1.63-4.19)
	max SOFA	1.46 (0.86-2.48)	1.71 (1.04-2.81)
Day 1 until Day 4	APACHE	1.61 (0.98-2.65)	2.63 (1.64-4.21)
	max SOFA	1.47 (0.89-2.42)	1.73 (1.06-2.84)

f) In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules (Rubin D.B.,Wiley New York 1987; Multiple Imputation for Nonresponse in Surveys).

g) The models also included the following predictors (HR results not shown): Antibiotic adequacy, Sepsis severity, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Gender.

Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models				
Model		**Hazard ratio (95 % confidence interval)**		
		Continuous predictors[f)] (HR[h)] per 1 SD)		
ΔPCT interval	**Score + Covariates[g)]**	**APACHE (1 SD=8.13)**	**max SOFA (1 SD=3.98)**	**Age (1 SD=16.18)**
Day 0 until Day 4	APACHE	1.25 (0.99-1.57)	----	1.59 (1.27-1.99)
	max SOFA	----	1.97 (1.53-2.53)	1.69 (1.35-2.10)
Day 1 until Day 4	APACHE	1.29 (1.04-1.62)	----	1.57 (1.25-1.96)
	max SOFA	----	2.00 (1.56-2.56)	1.67 (1.33-2.08)

h) HR=hazard ratio

The change of PCT over time can also be described by the ratio of PCT values from Day 4 and Day 0 (or Day 1):

$$PCT_{ratio} = \frac{PCT_{Day\ 4}}{PCT_{Day\ 0\ (or\ Day\ 1)}}$$

A decline of ΔPCT = 80 % translates into a PCT ratio of 0.2. The PCT ratio has values larger than 0.2 when the ΔPCT decline is below 80 % which is associated with a higher risk for cumulative 28-day all-cause mortality in patients diagnosed with severe sepsis or septic shock. Likewise, a PCT ratio below 0.2 indicates a lower risk for mortality within 28 days. On a continuous scale, the relative mortality risk for patients diagnosed with severe sepsis or septic shock is higher the larger the PCT ratio. The following tables list the hazard ratios for an increase by the factor 2 in PCT ratio, i.e. the relative increase in mortality risk for a patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio. For comparison, selected predictors are indicated with corresponding equivalents in standard deviation. For the patient location at Day 4, the risk estimate compares the hazards for patients with vs. without ICU care on Day 4.

Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models		
Model		**Hazard ratio (95 % confidence interval)**
		Binary predictors[f)]
ΔPCT interval	**Score + Covariates[g)]**	**Day 4 patient location (ICU vs. no ICU)**
Day 0 until Day 4	APACHE	2.57 (1.59-4.13)
	max SOFA	1.70 (1.03-2.80)
Day 1 until Day 4	APACHE	2.57 (1.60-4.11)
	max SOFA	1.74 (1.06-2.86)

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Hazard ratios for ΔPCT and selected predictors from multivariate Cox Regression Models					
Model		Hazard ratio (95 % confidence interval)			
		Continuous predictors[f] (HR per 2-fold increase in PCT ratio or per equivalent in SD)			
ΔPCT interval	Score + Covar[i),j)]	PCT ratio (2-fold increase)	APACHE (SD equiv[k)])[l)]	Max SOFA (SD equiv)[j)]	Age (SD equiv)[j)]
Day 0 until Day 4	APACHE	1.26 (1.12-1.42)	1.08 (0.96-1.22)	----	1.29 (1.15-1.45)
	max SOFA	1.20 (1.07-1.35)	----	1.37 (1.20-1.57)	1.32 (1.18-1.49)
Day 1 until Day 4	APACHE	1.29 (1.11-1.49)	1.19 (1.02-1.39)	----	1.37 (1.18-1.60)
	max SOFA	1.23 (1.06-1.44)	----	1.58 (1.33-1.87)	1.43 (1.23-1.67)

i) Covar = Covariates

j) The models also included the following predictors (HR results not shown): Antibiotic adequacy, Sepsis severity, Biological infection type, Clinical infection type, Positive blood culture, PCT on Day 0, Gender.

k) Equiv = Equivalent

l) A unit change of ΔPCT on log-2-scale corresponded to 0.52 SD of ΔPCT from Day 0 until Day 4 (0.69 SD for ΔPCT from Day 1 until Day 4). Accordingly, the reported ΔPCT hazard ratios refer to an increase of ΔPCT by a factor of 2. For comparability, hazard ratios of the other continuous predictors were estimated for the same fractional SDs, i.e. 0.52 or 0.69, respectively.

Cumulative 28-day all-cause mortality did not differ significantly for male vs. female patients ($\chi 2$ p-value = 0.84). Demographics with outcome information are shown below :

		Per-protocol population (N=598)			
Variable	Class	All N	Dead N	Alive N	Mortality %
Gender	Female	264	46	218	17.4
	Male	334	55	279	16.5
Age, years (categorized)	≤ 30	39	1	38	2.6
	> 30, ≤ 45	45	4	41	8.9
	> 45, ≤ 55	74	8	66	10.8
	> 55, ≤ 65	149	26	123	17.4
	> 65, ≤ 75	125	21	104	16.8
	> 75	166	41	125	24.7
Ethnicity	African-American	202	32	170	15.8
	Asian	7	0	7	0.0
	Caucasian	362	64	298	17.7
	Hispanic	23	5	18	21.7
	Other	4	0	4	0.0
Baseline PCT, ng/mL	< 0.5	125	19	106	15.2
	≥ 0.5, ≤ 2.0	104	13	91	12.5
	> 2.0	353	69	284	19.5
	Missing	16	0	16	0.0

Reference range

In a population of 282 self-reported healthy individuals, the 95th percentile, upper reference range limit was calculated at 0.08 ng/mL.

Analytical performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Precision

Precision was determined using Elecsys reagents, samples and controls in a protocol (EP05-A3) of the CLSI (Clinical and Laboratory Standards Institute): 2 runs per day in duplicate each for 21 days (n = 84). The following results were obtained:

cobas e 411 analyzer				
		Repeatability	Intermediate precision	% Total error
Sample	Mean (ng/mL)	CV %	CV %	
Human serum 1	0.037	16.7	24.3	57.02
Human serum 2	0.085	6.4	9.2	22.49
Human serum 3	0.121	4.2	6.2	14.95
Human serum 4	0.183	3.1	4.2	10.18
Human serum 5	0.242	2.2	3.6	8.67
Human serum 6	0.300	2.1	2.8	6.75
Human serum 7	0.400	2.0	3.2	7.68
Human serum 8	0.415	1.9	2.3	5.56
Human serum 9	1.52	1.6	2.2	5.36
Human serum 10	2.12	1.5	2.2	5.38
Human serum 11	2.93	1.4	2.4	5.76
Human serum 12	26.1	1.5	2.8	6.81
Human serum 13	44.6	1.6	2.8	6.69
Human serum 14	64.5	1.9	3.0	7.33
Human serum 15	97.6	1.7	2.4	5.79

Method comparison

2617 samples were run on the **cobas e** 411 analyzer and the predicate device (BRAHMS PCT sensitive KRYPTOR).

Passing Bablok[24]

Slope: 0.959 (95 % CI: 0.947; 0.972)

Intercept: -0.023 (95 % CI: -0.028; -0.018)

Coefficient: 0.989 (95 % CI: 0.988; 0.990)

Sample concentrations covered the measuring range of 0.02 - 100 ng/mL.

Analytical specificity

The Elecsys BRAHMS PCT assay on Elecsys and **cobas e** analyzers does not show any significant cross-reactions with the following substances, tested with PCT concentrations of approximately 0.4 ng/mL and 1.5 ng/mL (maximum tested concentration):

Substances	Non-interfering concentrations (ng/mL)
Human katacalcin	30
Human calcitonin	10
Human alpha-CGRP[m)]	10000
Human beta-CGRP	10000

m) Calcitonin Gene-Related Peptide

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