**Supplemental Digital Content**

**Supplement to: “Procalcitonin kinetics predicts mortality in sepsis patients: *Results from the multicenter Procalcitonin Monitoring Sepsis Study (MOSES)”***

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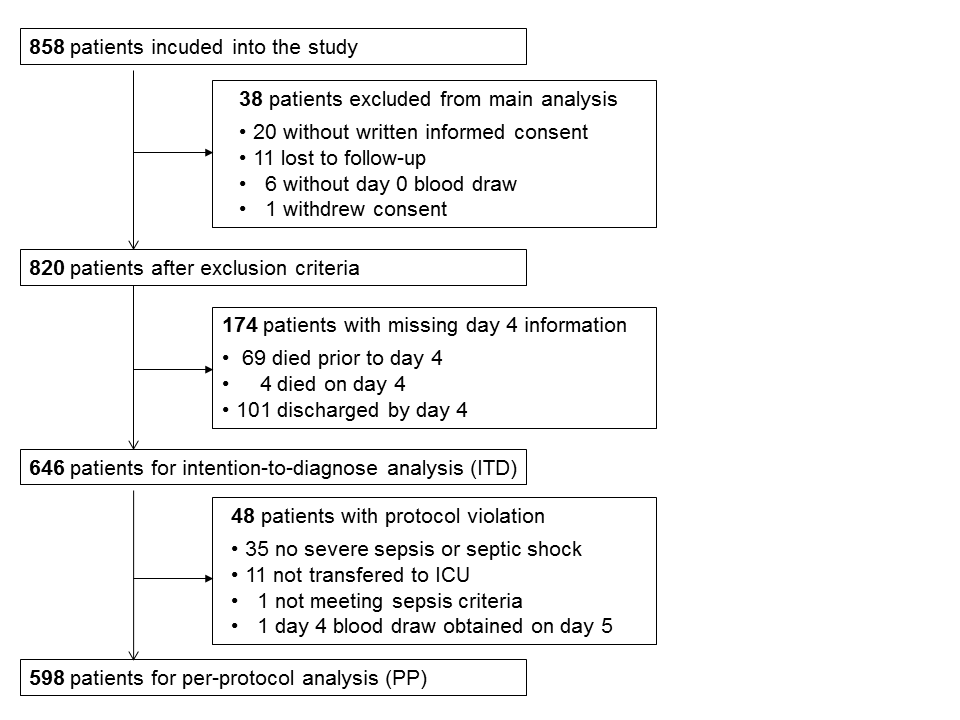
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# Figure S1 Patient flow

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# Details of the statistical approach and sample size calculations

We hypothesized *a priori* that an inability to decrease PCT by more than 80% from baseline to day4 would predict 28-day all-cause mortality. To test this hypothesis, we calculated cross tables, applied two-sided Fisher’s exact test and calculated prognostic measures such as sensitivity, specificity, negative and positive predictive value. We repeated this analysis and applied the Cochran-Mantel-Haenszel test with subgroups of patients discharged from the ICU at day4 and patients still being treated in the ICU at day4 and in patients with initial PCT values >2 µg/L and ≤2 µg/L. To assess the prognostic accuracy of a PCT decrease less than or equal to 80% , we calculated Cox proportional hazards regression adjusted for other predictors with time to death as the primary outcome of interest. We present hazard ratios (HR) and corresponding 95% confidence intervals (CIs) with and without adjustment for two predefined main outcome predictors (either APACHE II or maximum of baseline to day4 SOFA score)**,** as well as six *a priori* selected clinical parameters (appropriate antibiotic therapy, sepsis classification on admission, type of infection, clinical infection type, blood culture positivity, initial PCT level), and three additional predictors (age, gender, ICU care on day4) at the request of the FDA based on their independent analysis.

We also created Kaplan Meier curves for graphical display of data. The sample size of the study was determined (a) to validate clinically relevant 28-day mortality differences between patients with and without 80% PCT decrease, (b) to estimate prognostic performance with sufficient precision to predict 28-day mortality, and (c) to verify the added value of PCT decrease in multivariate Cox regression models as mentioned above. Therefore, the study was targeted for recruitment of a minimum of 80 events. With an estimated event rate of 10% we defined a total number of 800 patients. All statistical analyses were done with R version 3.1.2, deploying packages “mice” 2.22, “rms” 4.2-1, “survival” 2.37-7, and “Hmisc” 3.14-5 (1). Multiple imputation was conducted for missing PCT concentrations on days 1, 3, and 4. In contrast to single value imputation, multiple imputation allows to analyze all patients of the ITD population statistically while preserving the uncertainty of imputation.

We also performed several secondary exploratory analyses looking at the prognostic value of PCT at baseline through day 5, and on short term changes (i.e., baseline to day1).

Numeric factors are reported as mean values with standard deviations (SD; factor approximately normally distributed) or as median values with interquartile range (IQR, 25th to 75th percentile; factor non-normally distributed). All statistical testing was two-tailed and p-values below 5% were considered statistically significant.

# Table S1. Patient characteristics of the overall population, intention-to-diagnose and per protocol population

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All patients**  **n=820** | **ITD**  **n=646** | **Per Protocol**  **n=598** |
| **Socio-demographics** | | | |
| Female gender | 354 (43%) | 278 (43%) | 264 (44%) |
| Age [mean, SD, years] | 63.7 (±16.8) | 63.8(±16.3) | 64.1 (±16.2) |
| Ethnicity |  |  |  |
| African-American | 273 (33%) | 222 (34%) | 202 (32%) |
| Asian | 8 (1%) | 7 (1%) | 7 (1%) |
| Caucasian | 500 (61%) | 389 (60%) | 362 (61%) |
| Hispanic | 32 (4%) | 23 (4%) | 23 (4%) |
| **Comorbidities** | | | |
| Hypertension | 509 (62%) | 403 (62%) | 373 (62%) |
| Congestive Heart Failure | 145 (18%) | 112 (17%) | 107 (18%) |
| Coronary Artery Disease | 230 (28%) | 180 (28%) | 174 (29%) |
| Stroke/TIA | 99 (12%) | 85 (13%) | 81 (14%) |
| COPD | 140 (17%) | 109 (17%) | 102 (17%) |
| Diabetes | 277 (34%) | 218 (34%) | 208 (34%) |
| Liver Disease | 65 (8%) | 52 (8%) | 49 (8%) |
| Renal Disease | 112 (14%) | 84 (13%) | 80 (13%) |
| Malignancy | 199 (24%) | 151 (23%) | 146 (24%) |
| **Sepsis classification on admission** | | | |
| septic shock | 349 (43%) | 299 (46%) | 291 (49%) |
| severe sepsis | 402 (49%) | 347 (54%) | 307 (51%) |
| **Clinical infection type** | | | |
| community | 757 (92%) | 593 (92%) | 546 (91%) |
| nosocomial | 63 (8%) | 53 (8%) | 52 (9%) |
| **Positive Blood Culture** | | | |
| positive | 248 (30%) | 214 (33%) | 197 (33%) |
| **Microbiological result** | | | |
| fungal | 12 (2%) | 11 (2%) | 10 (2%) |
| gram negative | 272 (33%) | 227 (35%) | 215 (36%) |
| gram positive | 166 (20%) | 141 (22%) | 129 (22%) |
| **Antibiotic adequacy[[1]](#footnote-1)** | 705 (86%) | 543 (84%) | 503 (84%) |
| **Final diagnosis** | | | |
| confirmed infection | 662 (81%) | 542 (84%) | 504 (84%) |
| likely infection | 107 (13%) | 70 (11%) | 64 (11%) |
| other diagnosis | 51 (6%) | 34 (5%) | 30 (5%) |
| **Alive at day 28** | 636 (78%) | 539 (83%) | 497 (83%) |
| **Procalcitonin levels** | | | |
| Initial PCT [median, IQR, µg/L] | 4.2 (0.6-18.9) | 4.3 (0.6-20.0) | 4.6 (0.7-20.9) |
| < 0.5µg/L | 171 (21%) | 131 (20%) | 117 (20%) |
| ≥ 0.5µg/L and ≤ 2.0µg/L | 166 (20%) | 133 (21%) | 118 (20%) |
| > 2.0µg/L | 483 (59%) | 382 (59%) | 363 (61%) |
| **PCT kinetic from baseline to day 4** | | | |
| decrease ≤80% | 371 (45%) | 371 (57%) | 346 (58%) |
| decrease >80% | 203 (25%) | 203 (31%) | 188 (31%) |
| missing | 246 (30%) | 72 (11%) | 64 (10%) |
| **Patient location at day 4** | | | |
| ICU residency at day 4 | 278 (34%) | 276 (43%) | 265 (44%) |
| **Prognostic scores** [mean, SD] | | | |
| max SOFA (baseline - day 4) | 7.7 (±4.0) | 8.0 (±4.0) | 8.2 (±4.0) |
| APACHE II | 17.8 (±8.9) | 18.5 (±8.2) | 18.9 (±8.1) |
| **Lenght of stay**, [median, IQR, days] | | | |
| ICU stay | 3 (2-5) | 4 (2-6) | 4 (2-6) |
| total hospital stay | 9 (5-15) | 11 (7-17) | 11 (7-17) |

All numeric values with their mean and SD (or median and IQR) were rounded to one decimal place, all other values with their percentage were rounded to integer; APACHE II: Acute Physiology and Chronic Health Evaluation II; COPD: Chronic Obstructive Lung Disease; ICU: Intensive Care Unit; IQR: Inter Quartile Range; PCT: Procalcitonin; SD: standard deviation; max SOFA: maximum of Sequential Organ Failure Assessment; TIA: Transient Ischemic Attack

# Table S 2. Results of the multivariate Cox proportional hazard regression based on the intention-to-diagnose population including maximum SOFA score from baseline to day 4

The prognostic performance of ∆PCT (from baseline to day4) for the patient stratification of risk for mortality within the first 28 days is quantified by univariate and multivariate Cox proportional hazards regression. The multivariate model includes all factors listed below.

|  |  |  |  |
| --- | --- | --- | --- |
| **Factor** | **Comparison** | **Univariate hazard ratio** | **Multivariate hazard ratio** |
| PCT decrease from baseline to day 4 | high risk (≤ 80%) vs. low risk (> 80%) | 2.05 (1.30 - 3.24), p=0.00205 | 1.85 (1.11 - 3.08), p=0.019 |
| Max SOFA (highest value between baseline and day 4) | high risk (> median of 8) vs.  low risk (≤ median of 8) | 3.02 (2.03 - 4.50), p=0<0.001 | 2.24 (1.39 - 3.60), p=0.001 |
| Appropriate antibiotic therapy | no vs. yes | 1.46 (0.92 - 2.31), p=0.109 | 1.34 (0.81 - 2.22), p=0.256 |
| Sepsis class on admission | septic shock vs. severe sepsis | 1.21 (0.83 - 1.77), p=0.318 | 0.98 (0.65 - 1.47), p=0.912 |
| Type of infection | gram pos. vs. gram neg. | 0.94 (0.56 - 1.60), p=0.827 | 0.96 (0.56 – 1.66), p=0.897 |
| Type of infection | other vs. gram neg. | 1.02 (0.66 - 1.59), p=0.912 | 1.40 (0.85 - 2.33), p=0.189 |
| Type of infection | fungal vs. gram neg. | 2.32 (0.83 - 6.50), p=0.11 | 2.29 (0.77 – 6.83), p=0.136 |
| Clinical infection type | nosocomial vs. community | 0.76 (0.35 - 1.64), p=0.486 | 0.73 (0.34 – 1.58), p=0.426 |
| Blood culture | positive vs. negative | 0.98 (0.66 - 1.47), p=0.939 | 1.13 (0.71 – 1.79), p=0.610 |
| Initial PCT level | 2-fold higher \* | 1.02 ( 0.96 - 1.09), p=0.453 | 1.04 (0.96 – 1.12), p=0.373 |
| Age | increase by 5 years | 1.16 (1.09 - 1.24), p<0.0001 | 1.03 (1.02 - 1.05), p<0.0001 |
| Gender | female vs. male | 1.01 (0.69 - 1.48), p=0.972 | 0.96 (0.65 -1.41), p=0.835 |
| ICU residency at day 4 | yes vs. no | 3.18 (2.11 - 4.77), p<0.0001 | 2.05 (1.30 – 3.23), p=0.002 |

\* baseline PCT level in one patient vs baseline PCT level in another patient

ICU: Intensive Care Unit; PCT: Procalcitonin; max SOFA: maximum of Sequential Organ Failure Assessment

# Table S 3. Results of the multivariate Cox proportional hazard regression additionally including white blood cell count (WBC) based on the intention-to-diagnose population

The prognostic performance of ∆PCT (from baseline to day4) for the patient stratification of risk for mortality within the first 28 days is quantified by multivariate Cox proportional hazards regression. The multivariate model includes all factors listed below. PCT, WBC and SOFA score were integrated as numeric variables.

|  |  |  |
| --- | --- | --- |
| **Factor** | **Comparison** | **Multivariate hazard ratio** |
| Change in procalcitonin from baseline to day 4 (ratio day 4/baseline) | Increase by 1 standard deviation on log2 concentration scale\* | 1.39 (1.11 - 1.75), p=0.004 |
| Change in white blood cell count from baseline to day 4 (ratio day 4/baseline) | Increase by 1 standard deviation on log2 concentration scale\* | 1.07 (0.90 - 1.26), p=0.456 |
| Max SOFA (highest value between baseline and day 4) | Increase by 1 standard deviation on log2 concentration scale\* | 1.82 (1.42 – 2.34), p<0.0001 |
| Appropriate antibiotic therapy | no vs. yes | 1.20 (0.72 – 2.00), p=0.488 |
| Sepsis class on admission | septic shock vs. severe sepsis | 0.82 (0.54 - 1.24), p=0.340 |
| Type of infection | gram pos. vs. gram neg. | 0.82 (0.47 - 1.43), p=0.492 |
| Type of infection | other vs. gram neg. | 1.14 (0.68 - 1.90), p=0.624 |
| Type of infection | fungal vs. gram neg. | 2.02 (0.68 - 6.02), p=0.206 |
| Clinical infection type | nosocomial vs. community | 0.75 (0.34 - 1.64), p=0.466 |
| Blood culture | positive vs. negative | 1.11 (0.69 - 1.76), p=0.672 |
| Initial PCT level | Increase by 1 standard deviation on log2 concentration scale\* | 1.07 (0.82 - 1.40), p=0.618 |
| Age | increase by 5 years | 1.03 (1.02 - 1.05), p<0.0001 |
| Gender | female vs. male | 1.03 (0.70 - 1.52), p=0.891 |
| Intensive care unit residency at day 4 | yes vs. no | 1.56 (0.97 - 2.51), p=0.069 |

\* comparing value in one patient vs value in another patient

PCT: Procalcitonin; max SOFA: maximum of Sequential Organ Failure Assessment

# Table S 4. Results of the multivariate Cox proportional hazard regression based on the intention-to-diagnose patient population including change in SOFA score

The prognostic performance of ∆PCT (from baseline to day4) for the patient stratification of risk for mortality within the first 28 days is quantified by multivariate Cox proportional hazards regression. The multivariate model includes all factors listed below. PCT and SOFA score were integrated as numeric variables.

|  |  |  |
| --- | --- | --- |
| **Factor** | **Comparison** | **Multivariate hazard ratio** |
| Change in procalcitonin from baseline to day 4 (ratio day 4/baseline) | Increase by 1 standard deviation on log2 concentration scale\* | 1.43 (1.14 - 1.80), p=0.002 |
| Change in SOFA score from baseline to day 4 (ratio day 4/baseline) | Increase by 1 standard deviation on log2 concentration scale\* | 1.46 (1.15 – 1.86), p=0.002 |
| Appropriate antibiotic therapy | no vs. yes | 1.37 (0.82 - 2.27), p=0.224 |
| Sepsis class on admission | septic shock vs. severe sepsis | 1.21 (0.81 - 1.80), p=0.353 |
| Type of infection | gram pos. vs. gram neg. | 0.83 (0.48 - 1.45), p=0.518 |
| Type of infection | other vs. gram neg. | 1.25 (0.76 - 2.08), p=0.380 |
| Type of infection | fungal vs. gram neg. | 1.77 (0.60 - 5.26), p=0.301 |
| Clinical infection type | nosocomial vs. community | 0.82 (0.38 - 1.78), p=0.616 |
| Blood culture | positive vs. negative | 1.06 (0.67 - 1.69), p=0.791 |
| Initial PCT level | Increase by 1 standard deviation on log2 concentration scale\* | 1.26 (0.99 - 1.61), p=0.059 |
| Age | increase by 5 years | 1.03 (1.02 - 1.05), p<0.0001 |
| Gender | female vs. male | 1.09 (0.74 - 1.60), p=0.679 |
| Intensive care unit residency at day 4 | yes vs. no | 2.04 (1.31 - 3.19), p=0.002 |

\* comparing value in one patient vs value in another patient

PCT: Procalcitonin; max SOFA: maximum of Sequential Organ Failure Assessment

# Table S 5. Results of the univariate and multivariate Cox proportional hazard regression based on the per-protocol patient population

The prognostic performance of ∆PCT (from baseline to day4) for the patient stratification of risk for mortality within the first 28 days is quantified by univariate und multivariate Cox proportional hazards regression. The multivariate model includes all other factors listed below and either APACHE II or max SOFA score. Multivariate hazard ratios for the model including APACHE II score are shown below.

|  |  |  |  |
| --- | --- | --- | --- |
| **factor** | **comparison** | **Univariate hazard ratio** | **Multivariate hazard ratio** |
| PCT decrease from baseline to day 4 | high risk (≤ 80%) vs. low risk (> 80%) | 2.02 (1.27 - 3.23), p=0.0031 | 2.03 (1.19 - 3.44), p=0.009 |
| APACHE II | high risk (> median of 19) vs.  low risk (≤ median of 19) | 1.74 (1.17 - 2.58), p=0.006 | 0.94 (0.60 - 1.46), p=0.773 |
| Appropriate antibiotic therapy | no vs. yes | 1.59 (1.00 - 2.53), p=0.051 | 1.44 (0.86 - 2.40), p=0.164 |
| Sepsis class on admission | septic shock vs. severe sepsis | 1.19 (0.80 - 1.76), p=0.386 | 1.17 (0.77 - 1.76), p=0.461 |
| Type of Infection | gram pos. vs. gram neg. | 0.83 (0.48 - 1.45), p=0.522 | 0.92 (0.52 – 1.63), p=0.786 |
| Type of Infection | other vs. gram neg. | 0.99 (0.63 - 1.54), p=0.960 | 1.29 (0.78 - 2.15), p=0.320 |
| Type of Infection | fungal vs. gram neg. | 2.44 (0.87 - 6.84), p=0.090 | 1.95 (0.66 – 5.79), p=0.227 |
| clinical infection type | nosocomial vs. community | 0.76 (0.35 - 1.64), p=0.481 | 0.79 (0.36 – 1.72), p=0.556 |
| Blood culture | positive vs. negative | 1.05 (0.69 - 1.58), p=0.834 | 1.05 (0.65 – 1.69), p=0.836 |
| Initial PCT level | 2-fold higher \* | 1.03 ( 0.97 - 1.10), p=0.343 | 1.07 (0.99 – 1.15), p=0.108 |
| Age | increase by 5 years | 1.16 (1.08 - 1.24), p<0.0001 | 1.16 (1.08 - 1.24), p<0.0001 |
| Gender | female vs. male | 0.95 (0.64 - 1.40), p=0.782 | 0.91 (0.61 -1.35), p=0.645 |
| ICU residency at day 4 | yes vs. no | 3.45 (2.24 - 5.31), p<0.0001 | 3.11 (1.96 – 4.92), p<0.0001 |

\* baseline PCT level in one patient vs baseline PCT level in another patient

APACHE II: Acute Physiology and Chronic Health Evaluation II; ICU: Intensive Care Unit; PCT: Procalcitonin; max SOFA: maximum of Sequential Organ Failure Assessment

# Sensitivity analysis around baseline versus maximum baseline/day1 PCT levels

Following the instructions of the FDA, we explored whether there was a difference in predictive ability and diagnostic accuracy if a baseline or day1 PCT value was used instead of their maximum as the comparison value for the day4 change. Overall, results were similar to the main analysis when using PCT levels at baseline, day1 or the maximum level at both days (**Table S3**); thus, for simplicity reasons, the FDA has suggested that either day0 or day1 can be used as the reference and for the indication labeling when calculating a change over the 4 days and this is what we have reported in the manuscript.

# Table S 6. Comparison of prognostic performance of PCT decrease from day0, day1 or peak to day4 in the intention-to-diagnose population and stratified based on patients’ location on day4

Two-sided Fisher’s Exact Test analysis of ΔPCT test results (>80% or ≤80%) vs. vital status on day 28 yielded a significant association with mortality (p-value = 0.001) and was confirmed across ICU vs. non-ICU patient subgroups (based on hospital location at day 4 after initial diagnosis) by Cochran-Mantel-Haenszel Test (p-value = 0.013). Mortality rates and prognostic performance for the overall patient population and stratified by the need for continued ICU care on day 4 and/or the selection of day0 vs. day1 vs. peak value of day0/day1 as the baseline for the change in PCT calculation are as follows:

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **PCT baseline** | **Mortality PCT decrease > 80%** | **Mortality PCT decrease ≤ 80%** | | **NPV** | | **PPV** | **Sensitivity** | | | **Specificity** |
| **All patients (n=646, events =107)** | | | | | | | | | | |
| day0 | 10 (7-14) | 20 (16-24) | 90 (86-94) | | 20 (16-24) | | | 77 (70-85) | 39 (35-43) | |
| day1 | 12 (8-17) | 19 (15-23) | 88 (83-92) | | 19 (15-23) | | | 73 (64-81) | 38 (34-43) | |
| peak day0 / day1 | 12 (8-16) | 20 (16-25) | 88 (85-92) | | 20 (16-25) | | | 69 (60-78) | 47 (42-51) | |
| **Patients in the ICU at day4 (n=276, events =73)** | | | | | | | | | | |
| day0 | 19 (10-28) | 30 (23-36) | 81 (72-90) | | 30 (23-36) | | | 79 (70-89) | 32 (26-39) | |
| day1 | 21 (13-30) | 29 (22-36) | 79 (70-87) | | 29 (22-36) | | | 74 (64-84) | 35 (28-41) | |
| peak day0 / day1 | 20 (13-28) | 30 (23-37) | 80 (72-88) | | 30 (23-37) | | | 71 (60-81) | 42 (35-49) | |
| **Patients discharged from the ICU at day4 (n=370, events =34)** | | | | | | | | | | |
| day0 | 6 (2-10) | 12 (7-16) | 94 (90-98) | | 12 (7-16) | | | 73 (58-88) | 43 (37-48) | |
| day1 | 7 (3-11) | 11 (7-15) | 93 (89-97) | | 11 (7-15) | | | 70 (55-86) | 41 (35-46) | |
| peak day0 / day1 | 7 (3-10) | 12 (7-16) | 93 (90-97) | | 12 (7-16) | | | 64 (48-81) | 50 (44-55) | |

All values in % with 95%CI; ICU: Intensive Care Unit; PCT: Procalcitonin

# Table S7. Results stratification of patients based on absolute initial PCT levels Results of the intention-to-diagnose population

Stratification of patients based on absolute initial PCT levels (> or ≤ 2.0 µg/L) at day 0 revealed subgroups with particularly reduced or elevated mortality risk considering their hospital disposition on day 4 with significant Cochran-Mantel-Haenszel Test (p-value = 0.003).

|  |  |  |  |
| --- | --- | --- | --- |
| **Day4 Patient Location** | **PCT**  **at Day 0** | **28-day mortality**  **(%)** | |
| **ΔPCT4.0**  **> 80%** | **ΔPCT4.0**  **≤ 80%** |
| **ICU** | > 2.0 µg/L | 20 (11-30) | 32 (23-41) |
| ≤ 2.0 µg/L | 10 (0-28) | 26 (17-36) |
| **non ICU** | > 2.0 µg/L | 5 (2-9) | 19 (9-28) |
| ≤ 2.0 µg/L | 9 (0-21) | 8 (4-13) |

All values in % with 95% CI

# Figure S2a. 2x2 cross table and prognostic performance of PCT decrease in the whole per-protocol population

Mortality

ΔPCT decrease ≤ 80%: 20.4% (16.3-24.4%)

ΔPCT decrease > 80%: 10.7% (6.6-14.9%)

Sensitivity = 77.0% (68.8-85.3%)

Specificity = 38.8% (34.4-43.3%)

Pos Pred. Value = 20.4% (16.3-24.4%)

Neg. Pred. Value= 89.3% (85.1-93.4%)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Died** | **Lived** |  |
| **No strong ΔPCT4.0 decrease** | 78 | 304 | 382 |
| **Strong ΔPCT4.0 decrease** | 23 | 193 | 216 |
|  | 101 | 497 | 598 |

# Figure S2b: 2x2 cross table and prognostic performance of PCT decrease in subpopulation with ICU care on day 4

Mortality

ΔPCT decrease ≤ 80%: 30.4% (23.8-37.0%)

ΔPCT decrease > 80%: 19.4% (10.6-28.2%)

Sensitivity = 78.9% (69.5-88.4%)

Specificity = 32.6% (26.0-39.3%)

Pos Pred. Value = 30.4% (23.8-37.0%)

Neg. Pred. Value= 80.6% (71.8-89.4%)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Died** | **Lived** |  |
| **No strong ΔPCT4.0 decrease** | 57 | 130 | 187 |
| **Strong ΔPCT4.0 decrease** | 15 | 63 | 78 |
|  | 72 | 193 | 265 |

# Figure S2c: 2x2 cross table and prognostic performance of PCT decrease in subpopulation without ICU care on day 4

Mortality

ΔPCT decrease ≤ 80%: 10.8% (6.4-15.1%)

ΔPCT decrease > 80%: 5.8% (1.9-9.7%)

Sensitivity = 72.3% (56.0-88.7%)

Specificity = 42.8% (37.0-48.6%)

Pos Pred. Value = 10.8% (6.4-15.1%)

Neg. Pred. Value= 94.2% (90.3-98.1%)

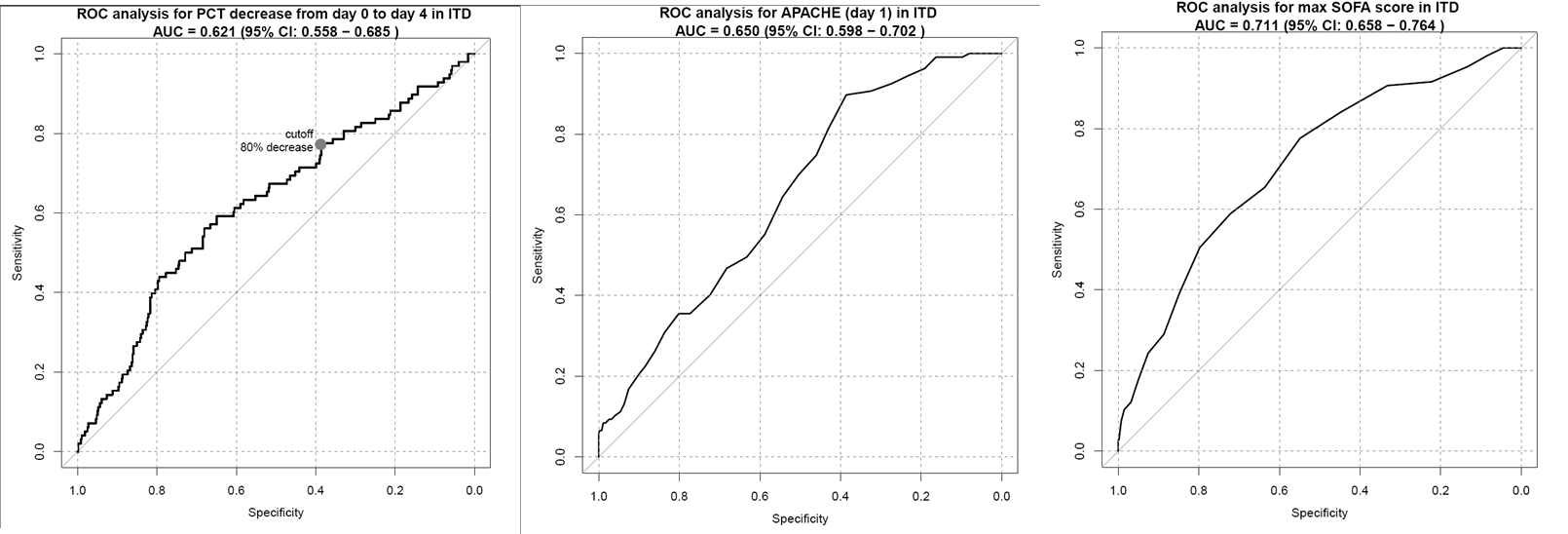
|  |  |  |  |
| --- | --- | --- | --- |
|  | **Died** | **Lived** |  |
| **No strong ΔPCT4.0 decrease** | 21 | 174 | 195 |
| **Strong ΔPCT4.0 decrease** | 8 | 130 | 138 |
|  | 29 | 304 | 333 |



# Figure S3. ROC analysis for selected predictors of 28-day mortality

ROC analysis (with AUC) on the ITD population computed for (1) PCT ratio day 4 vs day 0, (2) APACHE II and (3) maxSOFA as predictors of 28-day all-cause mortality. The AUCs were 0.62 for PCT, 0.65 for APACHE II and 0.71 for maxSOFA.

(1) (2) (3)



# Trial Definitions

## Definition of PCT decrease

PCT decrease or “ΔPCT” was defined: as the difference of PCT concentration[[2]](#footnote-2) between its

1. Maximum level of day0 [PCTday 0] and day1 [PCTday 1] or
2. Day 0 [PCTday 0] or
3. Day 1 [PCTday 1]

and the PCT concentration level on Day 4; [PCTday 4)].

Maximum ([PCTday 0] [PCTday 1]) – [PCTday 4]

ΔPCTPeak 0,1(%) = x 100 **or**

Maximum ([PCTday 0] [PCTday 1])

[PCTday 0] – [PCTday 4][PCTday 1] – [PCTday 4]

ΔPCT4.0 (%) = x 100 **or** ΔPCT4.1 (%) = x 100

[PCTday 0] [PCTday 1]

## Definition of Sepsis

according to ACCP/SCCM criteria (2, 3)

1. **Infection criteria**

Patients had to have a known infection or a suspected infection, as evidenced by one or more of the following:

* white cells in a normally sterile body fluid;
* perforated viscus;
* radiographic evidence of pneumonia in association with the production of purulent sputum;
* a syndrome associated with a high risk of infection (e.g. ascending cholangitis)

1. **SIRS criteria**

Patients had to meet at least 2 of the following four criteria:

* a core temperature of >38°C or <36°C (>100.4°F or <96.8°F);
* a heart rate of >90 beats/min , except in patients with a medical condition known to increase the heart rate or those receiving treatment that would prevent tachycardia,
* a respiratory rate >20 breaths/min or a PaCO2 of <32 mmHg or the use of mechanical ventilation for an acute respiratory process
* a white blood cell count >12,000/mm3 or <4000/mm3 or a differential count showing >10 percent immature neutrophils.

1. **Criteria for dysfunctional organs or systems**

Patients had to meet at least one of the following five criteria:

* cardiovascular system dysfunction

the arterial systolic blood pressure had to be ≤90 mmHg or the mean arterial pressure ≤70 mmHg for at least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status or the use of vasopressors in an attempt to maintain a systolic blood pressure of ≥90 mmHg or a mean arterial pressure of ≥70 mmHg;

* kidney dysfunction

urine output had to be <0.5 ml/kg of body weight/hr for 1 hour, despite adequate fluid resuscitation or increase of serum creatinine > 2× normal limit or >50% above known baseline in patients with chronic renal failure or need for renal replacement therapy;

* respiratory-system dysfunction

the ratio of PaO2/FiO2 had to be ≤250 (or SaO2/FiO2 ratio <180)in the presence of other dysfunctional organs or systems or ≤200 (or SaO2/FiO2 ratio <142) if the lung was the only dysfunctional organ;

* hematologic dysfunction

the platelet count had to be <80,000/mm3 or to have decreased by 50 percent in the 3 days preceding enrollment;

* in the case of unexplained metabolic acidosis, the pH had to be ≤7.30 or the base deficit had to be ≥5.0 mmol/liter in association with a plasma lactate level that was >1.5 times the upper limit of the normal value for the reporting laboratory.

**Sepsis**

Criteria I + II (clinical manifestations should be part of a direct systemic response to the presence of an infectious process with an alteration from baseline in the absence of other known causes for such abnormalities)

**Severe Sepsis**

Criteria I + II + III

**Septic shock**

Criteria I + II and state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mm Hg, a MAP <70 (table 1 in Levy *et al.* (2)), or a reduction in systolic blood pressure of >40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension.

## Sequential Organ Failure Assessment (SOFA score)

The organ dysfunction status will be determined as defined below (4). The worst values of each day will be entered into the CRF.

The SOFA score is composed of the sum of the points determined for the individual organ systems as listed below [[23](#_ENREF_23)]. A point score from zero through four will be allocated to each organ system. The following procedures will be utilized to determine the sub-scores of the individual components of the SOFA score:

**Cardiovascular System:**

Mean arterial pressure (MAP) or vasopressor use will determine the number of points for this sub-score. The lowest MAP value recorded over the previous 24h period will be entered onto the CRF; the highest dose of each catecholamine administered for > 1h in the previous 24 hour period will be entered into the CRF:

0 = MAP > 70 and no vasopressors

1 = MAP < 70 and no vasopressors

2 = dopamine < 5 µg/kg/min or dobutamine (any dose)

3 = dopamine > 5 to <15 mcg/kg/min or (nor) epinephrine < 0.1 mcg/kg/min .

4 = dopamine > 15 mcg/kg/min or (nor) epinephrine > 0.1 mcg/kg/min

MAP will be calculated using the following formula:

MAP = 2/3 diastolic pressure + 1/3 systolic pressure

**Pulmonary System:**

The PaO2/FiO2 (P/F) ratio will be used to determine this sub-score. The lowest PaO2 value and the highest FiO2 value over the previous 24h will be entered onto the CRF. If arterial blood gases are not available for a given calendar day or if the subject is no longer intubated but remains in the ICU with ventilatory support, the conversion tables (see below) will be used to determine the respective PaO2 or FiO2.

The values below refer to the ranges of P/F ratios (kPa).

0 = > 400 (> 53.2)

1 = 301-400 (39.9-53.1)

2 = 201-300 (26.6-39.8)

3 = 101-200 (13.3-26.5)

4 = < 100 (< 13.3)

**Coagulation System:**

Platelets will determine this sub-score. The lowest platelet count over the previous 24 hours will be entered into the CRF.

0 = > 150 x 103/mm3

1 = > 100-149 x 103/mm3

2 = > 50-99 x 103/mm3

3 = > 20-49 x 103/mm3

4 = < 20 x 103/mm3

**Renal System:**

Serum creatinine and urine output will determine this sub-score. The worst values will be entered into the CRF. Units are mg/dL (μmol/L).

0 = < 1.2 (<110)

1 = 1.2 - 1.9 (110 - 170)

2 = 2.0 - 3.4 (171 - 299)

3 = 3.5 - 4.9 (300 - 440) or urine output < 500 mL/24h.

4 = > 5.0 (> 441) or urine output is < 200 mL/24h

**Total Bilirubin:**

Total bilirubin will be determined at each study site and will be scored as described below. Units are mg/dL (μmol/L).

0 = < 1.2 (< 20)

1 = 1.2 - 1.9 (20 - 32)

2 = 2.0 - 5.9 (33 - 101)

3 = 6.0 - 11.9 (102 - 204)

4 = > 12 (> 205)

**Central Nervous System (CNS):**

According to the GCS

# References

1. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org/>. 2014.
2. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003, 31(4):1250-1256.
3. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992, 101(6):1644-1655.
4. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996, 22(7):707-710.

1. Assessed by chart review of independent infectious disease specialist, antibiotic administration will be considered adequate if at least one of the empiric antimicrobials has coverage against the pathogens isolated by antibiogram and if appropriate antibiotic therapy was started within 6 hours [↑](#footnote-ref-1)
2. Concentration of PCT is symboled as [PCT]. µg/L was used as standard measurement unit. [↑](#footnote-ref-2)