Supplementary online resource

Mortality and host response aberrations associated with transient and persistent acute kidney injury in critically ill patients with sepsis

Intensive Care Medicine

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References
## STROBE Statement

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|         | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 2       |
| 2       | Explain the scientific background and rationale for the investigation being reported | 5       |
| 3       | State specific objectives, including any prespecified hypotheses | 5       |
| 4       | Present key elements of study design early in the paper | 7       |
| 5       | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 7       |
| 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 7       |
|         | (b) For matched studies, give matching criteria and number of exposed and unexposed | 9       |
|         | +supplemental eMethods |         |
| 7       | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-8     |
| 8*      | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 7-8     |
| 9       | Describe any efforts to address potential sources of bias | 8-9     |
|         | +supplemental eMethods |         |
| 10      | Explain how the study size was arrived at | 7       |
| 11      | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 8-9     |
| 12      | (a) Describe all statistical methods, including those used to control for confounding | 8-9     |
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|         | (e) Describe any sensitivity analyses | 9       |
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| Participants | 13* | (a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed | 10 |
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|              |     | (b) Give reasons for non-participation at each stage                             |     |
|              |     | (c) Consider use of a flow diagram                                              | Supplemental eFigure 1 |
| Descriptive data | 14* | (a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders | 10 |
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| Outcome data | 15* | Report numbers of outcome events or summary measures over time                  | 11 |
| Main results | 16  | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 11 |
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| Other analyses | 17  | Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses | 11-13 |
| Discussion   |     | Summarize key results with reference to study objectives                        | 15 |
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| Limitations  | 19  | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 15-16 |
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| Generalizability | 21  | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 4 |

*Give information separately for exposed and unexposed groups.
eMethods

Ethics approval
All consecutive patients with sepsis older than 18 years of age and with an expected length of stay greater than 24 hours were included via an opt-out consent method approved by the institutional review boards of both hospitals (IRB No. 10-056C). Participants were notified of the study in writing by a brochure provided at ICU admission with attached an opt-out card that could be completed by the patient or by his or her legal representative in case of unwillingness to participate.

Biomarkers of the host response have been measured on left-over plasma obtained from blood drawn for routine patient monitoring and did not require any additional blood draw. The transcriptome analysis is based on the collection of 2.5 mL of whole blood in a PaxGene tube. The minimal risk for patient safety and the observational / non-interventional nature of the study allowed use of the opt-out method for patient inclusion.

Comorbidities
Cardiovascular compromise was defined as a medical history of congestive heart failure, chronic cardiovascular disease, myocardial infarction, peripheral vascular disease or cerebrovascular disease. Malignancy was defined as a medical history of either metastatic or not metastatic solid tumor, or hemodynamic malignancy.

Renal insufficiency was defined as a history of chronic renal insufficiency, or treatment with chronic intermittent hemodialysis or continuous ambulatory peritoneal dialysis. Respiratory insufficiency was defined as a history of chronic respiratory insufficiency, chronic obstructive pulmonary disease, or treatment at home with oxygen or ventilator support. Immune compromise was defined as a history of immune deficiency, human immunodeficiency virus (HIV) infection, acquired immune deficiency syndrome (AIDS), asplenia, or chronic use of corticosteroids, antineoplastic or other immune suppressive medications.

Chronic comorbid conditions were scored using the Charlson comorbidity index [1].

Disease severity and organ dysfunctions
Disease severity was determined using Acute Physiology and Chronic Health Evaluation (APACHE) IV score and a modified (m)SOFA score excluding central nervous system component [2]. The latter has been excluded from calculation of the SOFA score because a large proportion of patients received sedation in the ICU. The neurological component of the SOFA score could therefore not be accurately assessed. The non-renal mSOFA score reported in order to evaluate the impact of non-renal organ dysfunction on the evolution of AKI also excludes the central nervous system component.

Comorbidities, shock, acute respiratory distress syndrome (ARDS), and ICU-acquired complications were defined as described in the online resource.

Shock was defined by the use of vasopressors (norepinephrine, epinephrine or dopamine) for hypotension in a norepinephrine-equivalent dose of more than 0.1 µg/kg/min. Acute respiratory distress syndrome (ARDS) was prospectively defined using strict pre-set criteria [3].

Clinical and biological markers of renal function were recorded daily: we here report the highest value of serum creatinine and urea, the lowest value of bicarbonate measured every day, and the daily cumulative urine output. The results are provided for all patients irrespective of the use of renal replacement therapy.
Because the exact onset of organ dysfunction cannot always be determined in patients admitted to the ICU for sepsis (a large proportion of which being admitted directly from the emergency department), patients with AKI already present upon admission to the ICU were not excluded, and ICU-admission was deemed the onset of AKI.

In both centers involved in the current study, patients received renal replacement therapy for acute kidney injury (AKI) in accordance with the international KDIGO and sepsis guidelines [4, 5]. These criteria included life threatening indications (hyperkalemia, acidemia, pulmonary oedema), control of fluid balance, and trend in laboratory tests (rather than single urea and creatinine threshold alone).

**Intensive care unit (ICU)-acquired complications**

ICU-acquired AKI was defined as the onset of an episode of AKI more than 48 hours after admission to the ICU in the absence of AKI on admission, or more than 48 hours after the recovery of a previous episode of AKI [6]. ICU-acquired infection was defined as any new-onset infection starting more than 48 hours after ICU admittance, and for which the attending physician started a new antibiotic regimen. ICU-acquired ARDS was defined as ARDS diagnosed more than 48 hours after ICU admission.

**Biomarker assays**

All measurements were performed in EDTA plasma obtained on ICU-admission, day 2 and day 4 of ICU-stay. Interleukin (IL)-6, IL-8, IL-10, soluble intercellular adhesion molecule-1 (ICAM-1), soluble E-selectin and fractalkine were measured using FlexSet cytometric bead arrays (BD Biosciences, San Jose, CA) using a FACS Calibur (Becton Dickinson, Franklin Lakes, NJ). Angiopoietin-1, angiopoietin-2, protein C, antithrombin, matrix metalloproteinase (MMP)-8, neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (R&D Systems, Abingdon, UK), and D-dimer (Procartaplex, eBioscience, San Diego, CA) were measured by Luminex multiplex assay using a BioPlex 200 (BioRad, Hercules, CA). Platelet counts were determined by hemocytometry, prothrombin time (PT) and activated partial thromboplastin time (aPTT) by using a photometric method with Dade Innovin Reagent or by Dade Actin FS Activated PTT Reagent, respectively (Siemens Healthcare Diagnostics). Normal biomarker values were obtained from 27 age- and sex-matched healthy volunteers, from whom written consent was obtained, except for platelet counts, PT and aPTT (routine laboratory reference values).

**Microarray analysis and bioinformatics**

Whole blood was drawn from patients within 24 hours after the ICU admission in PAXgene™ tubes (Becton-Dickinson, Breda, the Netherlands) within 24 hours after ICU admission. PAXgene™ blood samples were also collected from 42 healthy controls (median age 35 years [interquartile range 30-63]; 57% male) after obtaining written informed consent. Total RNA was extracted using the PAXgene blood mRNA kit (Qiagen, Venlo, the Netherlands), according to manufacturer's instructions. Total RNA (RNA integrity number > 6.0) was processed and hybridized to the Affymetrix Human Genome U219 96-array and scanned by using the GeneTitan instrument at the Cologne Center for Genomics (CCG), Cologne, Germany, as described by the manufacturer (Affymetrix). Raw data scans (.CEL files) were read into the R language and environment for statistical computing (version 2.15.1; R Foundation for Statistical Computing, Vienna, Austria; [http://www.R-project.org/](http://www.R-project.org/)). Pre-processing and quality control were performed by using the Affy package (version 1.36.1) [7]. Array data were background corrected by robust multi-array average, quantiles-normalized and summarized by median polish using the expresso function. The resultant 49,386 log-transformed probe intensities were filtered by means of a 0.5 variance cut-off using the genefilter method [8] to recover 24,646 expressed probes in at least one sample. The occurrence of non-experimental chip-effects was evaluated by means of the
Surrogate Variable Analysis (R package version 3.4.0) and corrected by the empirical Bayes Method ComBat [9, 10]. The non-normalized and normalized MARS gene expression data sets are available at the Gene Expression Omnibus public repository of NCBI under the accession number GSE65682. The 24,646 probes were assessed for differential abundance across healthy subjects and patient samples using the limma method (version 3.36.5) [11]. Supervised analysis (comparison between pre-defined groups) was performed by moderated t-statistics. Throughout Benjamin-Hochberg (BH) multiple comparison adjusted probabilities, correcting for the 24,646 probes (false discovery rate < 5%), defined significance [12]. Ingenuity pathway analysis (Ingenuity Systems IPA, http://www.ingenuity.com) was used to identify the association with canonical signaling pathways, stratifying genes by over- and under-expressed patterns using fold changes. The ingenuity knowledgebase was selected as reference and human species specified. All other parameters were default. Multiple comparison adjusted (Benjamini-Hochberg) Fisher test probabilities <.05 defined significance.

Statistical analysis
Survival analyses were done by Kaplan-Meier estimation (with log-rank test) implemented in the Survival R package (version 2.44-1.1).

To investigate the independent association between the presence and the evolution of AKI and mortality, we performed a logistic regression controlling for potential confounding factors. The potential confounders included in the model were derived from literature review and expert opinion, and selected using a “change-in-estimate” approach [13], with a cut-off of 10%. The following variables were included in the model: age, RIFLE score upon admission, APACHE acute physiology score, source of infection, and modified Charlson comorbidity index [1] (excluding the contribution of age). Variables in the model were checked for collinearity by calculating the variance inflation factor. In addition, interactions between these variables and the evolution of AKI were investigated on a multiplicative scale. Model goodness of fit was evaluated via the Hosmer-Lemeshow test.

In order to determine the performance of individual plasma biomarkers in predicting the persistence of AKI at time of admission, we performed receiver operating characteristics (ROC) area-under-the-curve (AUC) analyses using the pROC package [14], with 95% confidence intervals (CI) calculated by bootstrap resampling (2000 stratified replicates).

Handling of missing data
After initial data collection, missing data or inconsistencies were checked by queries and added manually by the research team when possible.

In patient baseline characteristics and outcomes (Table 1), no data was missing, except for race (n= 13, 0.8%), antiplatelet drugs (n= 62, 4.0%), mSOFA score (n= 80, 5.2%), renal replacement therapy during the first 24 hours (n= 2, 0.1%), creatinine (n= 22, 1.4%), urea (n= 374, 24.2%), bicarbonate (n= 11, 0.7%), urine output (n= 2, 0.1%), and hospital length of stay (n= 1, 0.1%). Survival status up to one year after ICU-admission was established from the Municipal Personal Records Database, and was available for every patient in the current study.

In the logistic regression analysis, there was no missing value for any of the confounders considered for inclusion in the model (age, sex, RIFLE score upon admission, APACHE acute physiology score, presence of shock upon admission, use of mechanical ventilation at baseline, site of infection, Charlson comorbidity index, day-30 mortality).

The number and proportion of missing plasma biomarker data on admission, day 2 and day 4 is shown in the online resource eTable 9.

In the linear mixed effect analysis, missing observations were excluded listwise, assuming that data were missing completely at random or missing at random.
**Sensitivity and subgroup analyses**

In order to compare plasma biomarkers between groups of patients with different evolutions of AKI, a propensity score matching was performed, considering that the release of host response biomarkers is often proportional to disease severity during sepsis [15]. For this, we used a logistic regression implemented in the R package MatchIt version 3.0.2 ([http://gking.harvard.edu/matchit](http://gking.harvard.edu/matchit)) including variables associated with disease severity and other confounding variables at baseline. The propensity score included age, sex, modified Charlson comorbidity index, APACHE acute physiology score, a modified (m)SOFA score excluding the renal component, and the source of infection. In order to include as many patients with transient AKI as possible in the propensity matched analyses, patients from this group were first matched 1:3 to patients with a persistent AKI, using the nearest neighbor method and a caliper of 0.2 SD of the normally distributed propensity score. The procedure was repeated using the same parameters, in order to match patients with transient AKI to patients with no AKI. A similar propensity matching was performed to compare patients in whom the whole blood genomic host response was analyzed.

Sensitivity analyses were conducted including only patients still alive and present in the ICU after day-4.

To evaluate the impact of the severity of sepsis on the evolution of AKI, we performed additional subgroup analyses in patients with septic shock. These patients were further stratified according to the median duration of vasopressor infusion (< 52 hours, “short duration”, or ≥ 52 hours, “long duration”).

Various durations have been previously used to define AKI reversal. We therefore performed sensitivity analyses in order to investigate the impact of alternative cutoffs (72-hours and 96-hours) to distinguish between transient and persistent AKI.

Finally, because patients with less severe AKI could result in misclassifications due to minor changes in renal function, we conducted subgroup analysis in patients admitted with severe RIFLE I or F AKI.
eResults

Subgroup and sensitivity analyses

Multiple subgroup and sensitivity analyses were performed to assess the robustness of the analyses presented in the main manuscript.

Because RIFLE scores were not available up to day 4 in patients who died or were discharged earlier, we performed a sensitivity analysis in patients still alive and present in the ICU on day 4. The proportions of patients in each group were comparable to those in the whole cohort (Online resource eTable 10). In this subgroup, higher RIFLE scores remained associated with increased mortality at day 30 (Online resource eFigure 9a). Similarly, 30-day and 1-year mortality remained significantly higher in patients with persistent AKI, but not in patients with transient AKI (Online resource eTable 10, eFigure 9b). Finally, in a logistic regression analysis and after adjustment for confounding variables, persistent AKI remained independently associated with 30-day (OR 2.24, 95% CI 1.15 to 4.34; P= .018) and 1-year mortality (OR 2.16, 95% CI 1.12 to 4.17; P= .021, Online resource eTable 11).

Given that the presence and persistence of AKI were associated with different infection sources, higher APACHE IV and SOFA scores on admission, and considering that these variables can influence the host response, we matched patients with persistent, transient or no AKI on admission for age, sex, Charlson comorbidity index, APACHE acute physiology score, non-renal SOFA score and for the site of infection. This resulted in a cohort of 162 patients without AKI, 54 patients with transient AKI, and 116 patients with persistent AKI with comparable baseline characteristics and disease severity (Online resource eTable 12). In this matched cohort, host response aberrations largely remained in patients with persistent AKI, although not all differences were still significant, probably due to the lower sample size (Online resource eTable 13).

To further study the impact of sepsis severity on the host response associated with the course of AKI, we performed additional analyses in the subgroup of patients with shock. This subgroup entailed a higher proportion of patients with AKI (54%), most of which were persistent (83%) (Online resource eTable 14). The use of inotropes for persistent hypoperfusion was associated with higher prevalence of persistent AKI, possibly related to a more severe cardiovascular dysfunction as suggested by higher APACHE IV and mSOFA scores, higher vasopressors doses, lower mean arterial blood pressure and higher central venous pressure during the first 24 hours (Online resource eTables 14-15). The persistence of AKI remained associated with higher disease severity and specifically increased short- and log-term mortality (Online resource eTable 14, eFigure 10). Persistent AKI was associated with similar host response aberrations (Online resource eTables 16-17) and leukocyte transcriptome alterations remained minimally associated with the presence and evolution of AKI (Online resource eTable 18, eFigure 11). These alterations were not influenced by the duration of shock (Online resource eTables 19-24, eFigures 12-13).

In order to minimize the impact of moderate AKI severity on patient classification, we conducted additional analyses on the subgroup of patients with RIFLE I-F AKI upon admission. As expected, a vast majority (89%) of these patients developed a persistent AKI. In these patients with more severe AKI, all differences in outcomes, host response and leukocyte transcriptome remained (Online resources eTables 25-28, eFigure 14).

Because various durations have been previously used to define AKI reversal, we performed sensitivity analyses in order to investigate the impact of alternative cutoffs to distinguish between transient and persistent AKI. The use of 72- and 96-hour cutoffs resulted in small differences in the proportion of patients with persistent AKI (74% and 71% respectively), without major differences in patient characteristics and outcomes compared with 48-hour cutoff (Online resource eTables 29-30). The use of a 72-hour time point uncovered more differences in endothelial cell and coagulation activation biomarkers as well as differences in leukocyte transcriptome between patients without and transient AKI, without hampering differences between transient and persistent AKI (Online resource eTables 31-36, eFigures 15-16).
Finally, we measured host response plasma biomarkers in 632 ICU patients with a non-infectious admission diagnosis (Online resource eTables 37-38). Of these patients without sepsis 184 (29%) had AKI, of which 39 (21%) was transient and 145 (79%) was persistent. Host response plasma biomarkers revealed a similar association between systemic inflammation and loss of vascular integrity and the presence and persistence of AKI (Online resource eFigures 17-18). Comparison of blood leukocyte gene expression profiles from non-septic patients in whom array data were available (Online resource eTables 39-40, eFigure 19) also revealed minimal differences between patients without, transient or persistent AKI.
Supplemental tables

**eTable 1. Definition of acute kidney injury according to RIFLE and KDIGO criteria [4, 16]**

|                      | RIFLE                                      | KDIGO                                   | Urine output criteria (both scores) |
|----------------------|--------------------------------------------|------------------------------------------|-------------------------------------|
| **Risk**             | Increased sCreat x1.5 or GFR decrease > 25% | Stage 1 Increased sCreat x1.5 or ≥ 0.3 mg/dL increase | UO < 0.5 mL/kg/h x 6h               |
| **Injury**           | Increased sCreat x2 or GFR decrease > 50%  | Stage 2 Increased sCreat x2             | UO < 0.5 mL/kg/h x 12h              |
| **Failure**          | Increase sCreat x3 or GFR decrease 75 percent or sCreat ≥4 mg/dL | Stage 3 Increase sCreat x3 or sCreat ≥4 mg/dL or Initiation of RRT | UO < 0.3 mL/kg/h x 24h or Anuria x 12h |
| **Loss**             | Persistent ARF = complete loss of kidney function >4 weeks | -                                        | -                                   |
| **ESKD**             | End-stage kidney disease (>3 months)       | -                                        | -                                   |

Abbreviations: ARF, acute renal failure; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney disease: improving global outcomes; RIFLE, risk, injury, failure, loss and end-stage kidney disease; RRT, renal replacement therapy; sCreat, serum creatinine; UO, urine output.
### Table 2. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis, stratified according to the study center

| Demographics | AMC (n= 890) | UMCU (n= 655) | P Value |
|---------------|--------------|---------------|---------|
| Age, years    | 62 [49 - 71] | 63 [51 - 72] | .29     |
| Male sex      | 535 (60.1)   | 407 (62.1)   | .43     |
| Race, white   | 722 (82.3)   | 634 (96.8)   | <.001   |
| Medical admission | 652 (73.3) | 485 (74.0) | .77     |

### Chronic comorbidities

|                        | AMC          | UMCU         | P Value  |
|------------------------|--------------|--------------|----------|
| None                   | 358 (40.2)   | 126 (19.2)   | <.001    |
| Cardiovascular compromise | 197 (22.1) | 193 (29.5)   | .001     |
| Hypertension           | 191 (21.5)   | 207 (31.6)   | <.001    |
| Diabetes               | 136 (15.3)   | 135 (20.6)   | .007     |
| Liver cirrhosis        | 19 (2.1)     | 13 (2.0)     | >.99     |
| Immune compromise      | 139 (15.4)   | 197 (30.1)   | <.001    |

### Chronic medication

|                       | AMC          | UMCU         | P Value |
|-----------------------|--------------|--------------|---------|
| Diuretics             | 192 (21.6)   | 139 (21.2)   | .90     |
| ACE inhibitors / ARBs | 192 (21.6)   | 183 (27.9)   | .005    |
| Calcium-entry blockers| 110 (12.4)   | 98 (15.0)    | .15     |
| Beta-adrenergic blockers | 214 (24.0) | 171 (26.1)   | .37     |
| NSAIDs and Cox II inhibitors | 123 (13.8) | 54 (8.2)     | .001    |
| Oral antidiabetic drugs | 105 (11.8) | 90 (13.7)    | .28     |
| Corticosteroids       | 65 (7.3)     | 90 (13.7)    | <.001   |

### Severity at time of admission to ICU

|                       | AMC          | UMCU         | P Value |
|-----------------------|--------------|--------------|---------|
| APACHE IV score       | 71 [55 - 93] | 81 [64 - 101]| <.001   |
| Acute physiology score| 59 [44 - 79] | 68 [52 - 86] | <.001   |
| mSOFA score           | 7 [5 - 9]    | 6 [4 - 8]    | <.001   |
| Non-renal mSOFA score | 7 [4 - 8]   | 6 [4 - 8]    | <.001   |
| Shock                 | 478 (53.7)   | 306 (46.7)   | .007    |
| ARDS                  | 239 (26.9)   | 118 (18.0)   | <.001   |

### Therapy during the first 24h

|                       | AMC          | UMCU         | P Value |
|-----------------------|--------------|--------------|---------|
| Mechanical ventilation | 687 (77.2)  | 571 (87.2)   | <.001   |
| Vasopressors          | 602 (67.6)   | 377 (57.6)   | <.001   |
| Dose of Vasopressors (mg) | 8.9 [2.9 - 20] | 9.4 [3.7 - 19.2] | .84     |
| Inotropes             | 58 (6.5)     | 74 (11.3)    | .001    |
| Dose of inotropes (mg) | 165 [73.3]  | 151.5 [53.8 - 277.2] | .89     |
| RRT                   | 82 (9.2)     | 25 (3.8)     | <.001   |

### Nephrotoxic drugs (≥ one)

|                       | AMC          | UMCU         | P Value |
|-----------------------|--------------|--------------|---------|
| Aminoglycoside        | 258 (29.0)   | 23 (3.5)     | <.001   |
| Glycopeptide          | 156 (17.5)   | 40 (6.1)     | <.001   |
| Colloid               | 314 (35.3)   | 54 (8.2)     | <.001   |
| Otherb                | 66 (7.4)     | 75 (11.5)    | .007    |

### Source of infection

|                       | AMC          | UMCU         | P Value |
|-----------------------|--------------|--------------|---------|
| Pulmonary tract       | 431 (48.4)   | 349 (53.3)   | .06     |
| Abdominal             | 185 (20.8)   | 105 (16.0)   | <.001   |
| Cardiovascular        | 79 (8.9)     | 61 (9.3)     | .79     |
| Urinary tract         | 62 (7.0)     | 31 (4.7)     | .08     |
| CNS                   | 46 (5.2)     | 25 (3.8)     | 22      |
| Skin or soft tissue   | 34 (3.8)     | 18 (2.7)     | .26     |
| Otherc                | 48 (5.4)     | 56 (8.5)     | .018    |
| Unknown               | 5 (0.6)      | 10 (1.5)     | .07     |
**eTable 2 continued**

|                                | AMC (n= 890) | UMCU (n= 655) | P Value |
|--------------------------------|--------------|---------------|---------|
| **Renal function during the first 24 hours** |              |               |         |
| Creatinine, µmol/L             | 97 [68 - 155] | 96 [70 - 144] | .58     |
| Urea, mmol/L                   | 9.2 [5.8 - 13.9] | 8.1 [5.5 - 13.2] | .025    |
| Bicarbonate (minimal), mmol/L  | 20.3 [16.3 - 23.7] | 21.1 [17.2 - 25.3] | .001    |
| Urine output, mL               | 1690 [980 - 2738] | 1520 [985 - 2230] | .008    |

| **Admission RIFLE score**      |              |               | .001    |
| None                           | 562 (63.1)   | 458 (69.9)    |         |
| At risk                        | 95 (10.7)    | 75 (11.5)     |         |
| Injury                         | 103 (11.6)   | 68 (10.4)     |         |
| Failure                        | 130 (14.6)   | 54 (8.2)      |         |

| **Evolution of AKI**           |              |               | .002    |
| No AKI                         | 525 (59.0)   | 443 (67.6)    |         |
| Transient AKI                  | 68 (7.6)     | 38 (5.8)      |         |
| Persistent AKI                 | 297 (33.4)   | 174 (26.6)    |         |

| **Outcome**                   |              |               |         |
| Duration of initial MV, days  | 2 [1 - 5]    | 3 [1 - 7]     | <.001   |
| Recurrence of MV              | 37 (4.2)     | 20 (3.1)      | .28     |
| MV-free days \(^d\)           | 84 [11 - 89] | 81 [11 - 88]  | .004    |
| Use of RRT \(^d\)             | 129 (14.5)   | 64 (9.8)      | .006    |
| RRT-free days \(^d\)          | 90 [17 - 90] | 90 [20 - 90]  | .44     |

| **Complications**             |              |               |         |
| None                           | 796 (89.4)   | 569 (86.9)    | .13     |
| ICU-acquired AKI               | 42 (4.7)     | 31 (4.7)      | >.99    |
| ICU-acquired ARDS             | 17 (1.9)     | 16 (2.4)      | .48     |
| ICU-acquired infection        | 59 (6.6)     | 54 (8.2)      | .24     |
| ICU length of stay, days      | 4 [3 - 8]    | 5 [3 - 10]    | .002    |
| Hospital length of stay, days | 15 [7 - 31]  | 16 [8 - 32]   | .24     |
| ICU-mortality                 | 173 (19.4)   | 127 (19.4)    | >.99    |
| 30-day mortality              | 244 (27.4)   | 177 (27.0)    | .91     |
| 60-day mortality              | 292 (32.8)   | 214 (32.7)    | >.99    |
| 90-day mortality              | 319 (35.8)   | 233 (35.6)    | .96     |
| 1-year mortality              | 387 (43.5)   | 296 (45.2)    | .53     |
| ICU-free days \(^d\)          | 82 [11 - 87] | 79 [11 - 86]  | .16     |

**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; AMC, Academic medical Center Amsterdam; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component); UMCU, University Medical Center, Utrecht.

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Wilcoxon rank-sum test. Associations between categorical variables were tested using the Fisher’s exact test.

* Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

\(^{a}\) Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

\(^{b}\) Other sites of infection: Infections of bones and joints (n=19), Oral infections (n=8), Postoperative wound infections (n=20), Upper respiratory tract infections (n=20), Viral systemic infections (n=6), Endometritis (n=4), Other (n=27).

\(^{c}\) Between inclusion and day-90.

\(^{d}\) Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
**eTable 3. Causative pathogens in patients admitted with sepsis stratified according to the presence and evolution of acute kidney injury**

|                   | No AKI (n = 968) | Transient AKI (n = 106) | Persistent AKI (n = 471) | P Value |
|-------------------|------------------|-------------------------|--------------------------|---------|
| Gram-positive     | 278 (28.7)       | 41 (38.7)               | 162 (34.4)               | .020    |
| Gram-negative     | 272 (28.1)       | 36 (34.0)               | 163 (34.6)*              | .030    |
| Yeast / fungi     | 49 (5.1)         | 9 (8.5)                 | 40 (8.5)*                | .025    |
| Virus             | 46 (4.8)         | 1 (0.9)                 | 21 (4.5)                 | .19     |
| Other*            | 50 (5.2)         | 2 (1.9)                 | 29 (6.2)                 | .20     |
| Multiple pathogens| 139 (14.4)       | 21 (19.8)               | 93 (19.7)*               | .020    |
| Unknown           | 379 (39.2)       | 35 (33.0)               | 135 (28.7)*              | <.001   |

Abbreviation: AKI, acute kidney injury.

Data presented as n (%). Associations between categorical variables were tested using the Fisher's exact test.

* P values were adjusted for multiple testing using the Bonferroni correction.

* Significant vs no AKI, using a pairwise test for a multi-level 2-dimensional matrix.

† Significant vs Transient AKI, using a pairwise test for a multi-level 2-dimensional matrix.

* Other causative pathogens: anaerobic bacteria, polymicrobial or fecal flora, *Mycobacterium* spp., *Mycoplasma pneumoniae*, *Rickettsia rickettsii*, other pathogens.
**eTable 4. Logistic regression analysis evaluating the influence of the evolution of acute kidney injury on 1-year mortality**

|                      | Whole cohort |          |          |
|----------------------|--------------|----------|----------|
|                      | Odds Ratio   | P Value  | Wald test|
|                      | (95% CI)     |          | χ² (df), P |
| **Crude model**      |              |          |          |
| No AKI               | 1.00 (reference) | -       | 59.0 (2), P<.001 |
| Transient AKI        | 1.00 (0.66-1.51) | >.99    |          |
| Persistent AKI       | 2.38 (1.90-2.98) | <.001   |          |
| **Adjusted model**   |              |          |          |
| No AKI               | 1.00 (reference) | -       | 8.31 (2), P=.02 |
| Transient AKI        | 1.23 (0.60-2.49) | .57     |          |
| Persistent AKI       | 2.10 (1.12-3.92) | .020    |          |

Abbreviation: AKI, acute kidney injury, CI confidence interval.

a Unadjusted model.
b Adjusted for age, admission RIFLE score, APACHE acute physiology score, source of infection, and modified-Charlson comorbidity index (omitting the age parameter).
| Demographics | No AKI (n = 497) | Transient AKI (n = 67) | Persistent AKI (n = 302) | P Value |
|--------------|-----------------|------------------------|--------------------------|---------|
| Age, years   | 61 [48-70]      | 66 [53-72]             | 63 [54-72]*              | .001    |
| Male sex     | 306 (61.6)      | 34 (50.7)              | 170 (56.3)               | .12     |
| Race, white  | 426 (85.9)      | 56 (83.6)              | 264 (88.6)               | .41     |
| Medical admission | 371 (74.6) | 46 (68.7)              | 222 (73.5)               | .57     |
| Chronic comorbidities | | | | |
| None         | 159 (32.0)      | 21 (31.3)              | 85 (28.1)                | .52     |
| Cardiovascular compromise | 114 (22.9) | 18 (26.9)              | 80 (26.5)                | .47     |
| Hypertension | 111 (22.3)      | 26 (38.8)*             | 76 (25.2)                | .013    |
| Diabetes     | 78 (15.7)       | 12 (17.9)              | 56 (18.5)                | .56     |
| Liver cirrhosis | 10 (2.0)  | 2 (3.0)                | 10 (3.3)                 | .51     |
| Immune compromise | 109 (21.9) | 10 (14.9)              | 65 (21.5)                | .42     |
| Malignancy   | 105 (21.1)      | 11 (16.4)              | 78 (25.8)                | .14     |
| Charlson comorbidity index | 3 [1-5] | 3 [2-5]                | 3 [2-5]*                 | .024    |
| Chronic medication | | | | |
| Diuretics    | 90 (18.1)       | 18 (26.9)              | 78 (25.8)*               | .019    |
| ACE inhibitors / ARBs | 101 (20.3) | 16 (23.9)              | 81 (26.8)                | .10     |
| Calcium-entry blockers | 58 (11.7) | 14 (20.9)              | 41 (13.6)                | .10     |
| Beta-adrenergic blockers | 105 (21.1) | 16 (23.9)              | 77 (25.5)                | .35     |
| NSAIDs and Cox II inhibitors | 61 (12.3) | 11 (16.4)              | 40 (13.2)                | .63     |
| Oral antidiabetic drugs | 50 (10.1) | 9 (13.4)               | 42 (13.9)                | .23     |
| Corticosteroids | 62 (12.5) | 6 (9.0)                | 30 (9.9)                 | .45     |
| Inotropes     | 16 (3.2)        | 3 (4.5)                | 50 (16.6)*               | <.001   |
| Dose of inotropes (mg)a | 159.3 [44.4 - 281.5] | 218.3 [180.7 - 566.5] | 207.0 [82.2 - 328.2] | .51     |
| Respiratory support | | | | |
| Mechanical ventilation | 427 (85.9) | 56 (83.6)              | 255 (84.4)               | .79     |
| Vasopressors  | 295 (59.4)      | 48 (71.6)              | 263 (87.1)*              | <.001   |
| Dose of vasopressors (mg)a | 5.9 [2.2 - 13.9] | 11.7 [4.6 - 20.2]* | 16.0 [5.7 - 36.9]* | <.001   |
| Inotropes     | 16 (3.2)        | 3 (4.5)                | 50 (16.6)*               | <.001   |
| Dose of inotropes (mg)a | 159.3 [44.4 - 281.5] | 218.3 [180.7 - 566.5] | 207.0 [82.2 - 328.2] | .51     |
| RRT           | 4 (0.8)         | 3 (4.5)                | 74 (24.6)*               | <.001   |
| Nephrotoxic drugs (≥ one) | 223 (44.9) | 34 (50.7)              | 203 (67.2)*              | <.001   |
| Aminoglycoside | 86 (17.3)   | 16 (23.9)              | 91 (30.1)*               | <.001   |
| Glycopeptide  | 60 (12.1)       | 5 (7.5)                | 59 (19.5)*               | .004    |
| Colloid       | 110 (22.1)      | 22 (32.8)              | 129 (42.7)*              | <.001   |
| Other b       | 42 (8.5)        | 4 (6.0)                | 28 (9.3)                 | .73     |
| Source of infection | | | | |
| Pulmonary tract | 298 (60.0) | 31 (46.3)              | 109 (36.1)*              | <.001   |
| Abdominal     | 77 (15.5)       | 20 (29.9)*             | 81 (26.8)*               | <.001   |
| Cardiovascular | 48 (9.7)      | 5 (7.5)                | 42 (13.9)                | .12     |
| Urinary tract | 20 (4.0)        | 4 (6.0)                | 28 (9.3)*                | .009    |
| CNS           | 22 (4.4)        | 1 (1.5)                | 6 (2.0)                  | .14     |
| Skin or soft tissue | 13 (2.6) | 3 (4.5)                | 22 (7.3)*                | .007    |
| Other c       | 19 (3.8)        | 3 (4.5)                | 8 (2.6)                  | .51     |
| Unknown       | 0 (0.0)         | 0 (0.0)                | 6 (2.0)                  | .006    |

*eTable 5 continued*
| Renal function during the first 24 hours | No AKI | Transient AKI | Persistent AKI | P Value |
|--------------------------------------|--------|---------------|---------------|---------|
| **Creatinine, μmol/L**               | 79 [61-103] | 128 [92-168]* | 174 [127-246]*† | <.001 |
| **Urea, mmol/L**                     | 6.9 [4.7-10.1] | 10.8 [8.4-17.8]* | 13.3 [9.2-19.1]* | <.001 |
| **Bicarbonate (minimal), mmol/L**    | 22.1 [18.9-25.8] | 18.9 [17.2-22.8]* | 16.2 [13.2-19.7]† | <.001 |
| **Urine output, mL**                 | 1820 [1315-2750] | 1370 [919-2369]* | 958 [469-1573]*† | <.001 |

**Outcome**

| Duration of initial MV, days | 2 [1-7] | 4 [2-7] | 3 [1-8] | .21 |
| Recurrence of MV | 13 (2.6) | 5 (7.5) | 16 (5.3) | .050 |
| MV-free days | 84 [29-88] | 83 [30-88] | 51 [2-85]*† | <.001 |
| Use of RRT | 18 (3.6) | 4 (6.0) | 118 (39.1)*† | <.001 |
| RRT-free days | 90 [44-90] | 90 [40-90] | 63 [4-90]*† | <.001 |
| Complications | None | 430 (86.5) | 57 (85.1) | 254 (84.1) | .64 |
| ICU-acquired AKI | 41 (8.2) | 3 (4.5) | 11 (3.6)* | .028 |
| ICU-acquired ARDS | 15 (3.0) | 1 (1.5) | 8 (2.6) | .77 |
| ICU-acquired infection | 32 (6.4) | 8 (11.9) | 38 (12.6)* | .009 |
| ICU length of stay, days | 5 [3-9] | 7 [4-12]* | 6 [3-12]* | .007 |
| Hospital length of stay, days | 17 [10-33] | 21 [12-38] | 17 [7-38] | .10 |
| ICU-mortality | 64 (12.9) | 8 (11.9) | 111 (36.8)*† | <.001 |
| 30-day mortality | 107 (21.5) | 13 (19.4) | 123 (40.7)*† | <.001 |
| 60-day mortality | 139 (28.0) | 19 (28.4) | 145 (48.0)*† | <.001 |
| 90-day mortality | 157 (31.6) | 20 (29.9) | 156 (51.7)*† | <.001 |
| 1-year mortality | 202 (40.6) | 27 (40.3) | 179 (59.3)*† | <.001 |
| ICU-free days | 82 [33-86] | 81 [33-86] | 53 [0-83]*† | <.001 |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson \( \chi^2 \) test or the Fisher’s exact test when appropriate. \( P \) value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

a Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

b Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

c Other sites of infection: Infections of bones and joints (n=8), Oral infections (n=3), Postoperative wound infections (n=4), Upper respiratory tract infections (n=7), Viral systemic infections (n=4), Other (n=4).

d Between inclusion and day-90.

e Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
# General mixed model analysis of the change in biomarker plasma levels over the first four days of ICU-stay, stratified according to the presence and evolution of AKI

| Biomarker             | No AKI                        | Transient AKI                     | Persistent AKI                     | P Value (time x group) |
|-----------------------|-------------------------------|-----------------------------------|------------------------------------|------------------------|
| **Biomarkers of renal function** |                               |                                   |                                    |                        |
| NGAL                  | Rate of change (SE) -0.06 (0.01) | -0.14 (0.02)*                     | -0.05 (0.01)†                     | 0.001                  |
|                       | % change (SE) -20.92% (-0.20)   | -43.14% (-1.21)                   | -18.65% (-0.22)                   |                        |
| Cystatin C            | Rate of change (SE) 0.05 (0.01) | -0.01 (0.02)                      | 0.03 (0.01)                       | 0.09                   |
|                       | % change (SE) 19.88% (0.16)     | -2.58% (-0.06)                    | 12.63% (0.13)                     |                        |
| **Inflammatory responses** |                               |                                   |                                    |                        |
| IL-10                 | Rate of change (SE) -0.23 (0.02) | -0.43 (0.05)*                     | -0.35 (0.03)*                     | <0.001                 |
|                       | % change (SE) -60.59% (-1.97)   | -82.05% (-8.98)                   | -74.89% (-3.66)                   |                        |
| IL-6                  | Rate of change (SE) -0.37 (0.03) | -0.60 (0.07)*                     | -0.61 (0.04)*                     | <0.001                 |
|                       | % change (SE) -77.31% (-4.08)   | -90.85% (-15.79)                  | -91.28% (-8.26)                   |                        |
| IL-8                  | Rate of change (SE) -0.21 (0.02) | -0.34 (0.05)*                     | -0.34 (0.02)*                     | <0.001                 |
|                       | % change (SE) -56.85% (-1.59)   | -74.41% (-6.34)                   | -73.88% (-3.17)                   |                        |
| MMP-8                 | Rate of change (SE) -0.17 (0.03) | -0.35 (0.07)                      | -0.19 (0.04)                      | 0.06                   |
|                       | % change (SE) -48.53% (-1.89)   | -75.50% (-9.69)                   | -53.90% (-2.75)                   |                        |
| WBC count             | Rate of change (SE) -0.04 (0.01) | -0.01 (0.03)                      | 0.04 (0.01)*                      | <0.001                 |
|                       | % change (SE) -16.20% (-0.20)   | -4.92% (-0.14)                    | 18.39% (0.24)                     |                        |
| **Endothelial cell activation** |                               |                                   |                                    |                        |
| Fractalkine           | Rate of change (SE) -0.02 (0.01) | -0.05 (0.03)                      | 0.04 (0.02)*†                     | 0.01                   |
|                       | % change (SE) -5.97% (-0.08)    | -18.51% (-0.69)                   | 18.00% (0.29)                     |                        |
| sE-Selectin           | Rate of change (SE) -0.05 (0.01) | -0.14 (0.04)*                     | -0.10 (0.02)*                     | 0.008                  |
|                       | % change (SE) -16.61% (-0.26)   | -43.59% (-2.00)                   | -32.45% (-0.69)                   |                        |
| sICAM-1               | Rate of change (SE) 0.05 (0.01)  | 0.00 (0.03)                       | 0.05 (0.01)                       | 0.24                   |
|                       | % change (SE) 19.74% (0.19)     | -0.14% (0.00)                     | 21.29% (0.26)                     |                        |
| Angiopoietin-1        | Rate of change (SE) -0.05 (0.02) | -0.09 (0.04)                      | -0.12 (0.02)*                     | 0.018                  |
|                       | % change (SE) -18.78% (-0.33)   | -31.58% (-1.50)                   | -39.00% (-0.98)                   |                        |
| Angiopoietin-2        | Rate of change (SE) -0.00 (0.03) | -0.08 (0.07)                      | -0.06 (0.04)                      | 0.26                   |
|                       | % change (SE) 2.00% (0.06)      | -27.91% (-2.33)                   | -21.44% (-0.86)                   |                        |
| ANG2:ANG1             | Rate of change (SE) -0.06 (0.03) | -0.01 (0.08)                      | 0.06 (0.04)                       | 0.87                   |
|                       | % change (SE) 27.17% (0.81)     | 5.93% (0.49)                      | 29.24% (1.09)                     |                        |
### eTable 6 continued

| Biomarker              | No AKI | Transient AKI | Persistent AKI | \( P \) Value (time x group) |
|------------------------|--------|---------------|----------------|-----------------------------|
| **Coagulation activation** |        |               |                |                             |
| D-dimer                |        |               |                |                             |
| Rate of change (SE)    | 0.03 (0.01) | 0.00 (0.04) | 0.05 (0.02) | 0.42                        |
| % change (SE)          | 14.12% (0.18) | -1.38% (-0.05) | 21.09% (0.34) |                             |
| Protein C              |        |               |                |                             |
| Rate of change (SE)    | 0.03 (0.01) | 0.02 (0.02) | 0.00 (0.01)* | 0.020                       |
| % change (SE)          | 13.76% (0.10) | 7.22% (0.14) | -1.17% (-0.01) |                             |
| Antithrombin           |        |               |                |                             |
| Rate of change (SE)    | 0.05 (0.01) | 0.08 (0.02) | 0.03 (0.01) | 0.09                        |
| % change (SE)          | 23.15% (0.19) | 38.92% (0.74) | 13.16% (0.14) |                             |
| PT                     |        |               |                |                             |
| Rate of change (SE)    | -0.03 (0.00) | -0.06 (0.01)* | -0.06 (0.00)* | <0.001                      |
| % change (SE)          | -11.22% (-0.04) | -19.80% (-0.21) | -20.92% (-0.11) |                             |
| aPTT                   |        |               |                |                             |
| Rate of change (SE)    | -0.03 (0.01) | -0.03 (0.02) | -0.06 (0.01) | 0.08                        |
| % change (SE)          | -11.07% (-0.09) | -12.73% (-0.27) | -19.91% (-0.19) |                             |
| Platelets              |        |               |                |                             |
| Rate of change (SE)    | 0.01 (0.01) | -0.02 (0.02) | -0.05 (0.01)*† | <0.001                      |
| % change (SE)          | 2.90% (0.02) | -6.39% (-0.10) | -19.11% (-0.17) |                             |

Overall \( P \) values are derived from the linear mixed model in which the group and the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between individual group trajectories are derived from the linear mixed model.

* Trajectory significantly different vs. no AKI
† Trajectory significantly different vs. Transient AKI
Table 7. Receiver operating characteristic analysis of host response plasma biomarkers for the prediction of the evolution toward persistent AKI

| Biomarker                  | AUC (95% CI)  |
|----------------------------|---------------|
| **Inflammatory responses** |               |
| IL-10                      | 0.63 (0.56 - 0.69) |
| IL-6                       | 0.58 (0.50 - 0.64) |
| IL-8                       | 0.62 (0.56 - 0.69) |
| MMP-8                      | 0.51 (0.44 - 0.59) |
| **Endothelial cell activation** |           |
| Fractalkine                | 0.65 (0.58 - 0.72) |
| sE-selectin                | 0.52 (0.44 - 0.60) |
| sICAM-1                    | 0.58 (0.50 - 0.65) |
| Ang-1                      | 0.63 (0.56 - 0.70) |
| Ang-2                      | 0.62 (0.55 - 0.69) |
| Ang-2:Ang-1                | 0.67 (0.60 - 0.73) |
| **Coagulation activation** |               |
| D-dimer                    | 0.59 (0.51 - 0.66) |
| Protein C                  | 0.56 (0.48 - 0.64) |
| Antithrombin               | 0.48 (0.41 - 0.56) |
| PT                         | 0.65 (0.58 - 0.73) |
| aPTT                       | 0.67 (0.58 - 0.76) |
| Platelets                  | 0.65 (0.58 - 0.72) |
| **Biomarkers of renal function** |          |
| Cystatin C                 | 0.67 (0.60 - 0.74) |
| NGAL                       | 0.56 (0.48 - 0.64) |

Abbreviations: ANG, angiopoietin; aPTT, activated partial thromboplastin time; AUC, area under the curve; CI, confidence interval; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.
Table 8. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis and with blood genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury

|                                | No AKI (n = 225) | Transient AKI (n = 36) | Persistent AKI (n = 131) | P Value |
|--------------------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**               |                  |                        |                          |         |
| Age, years                     | 63 [49-70]       | 63 [50-74]             | 64 [56-72]               | .19     |
| Male sex                       | 130 (57.8)       | 17 (47.2)              | 75 (57.3)                | .50     |
| Race, white                     | 184 (82.5)       | 31 (86.1)              | 112 (87.5)               | .44     |
| Medical admission               | 166 (73.8)       | 25 (69.4)              | 90 (68.7)                | .56     |
| **Chronic comorbidities**      |                  |                        |                          |         |
| None                            | 74 (32.9)        | 12 (33.3)              | 45 (34.4)                | .96     |
| Cardiovascular compromise       | 47 (20.9)        | 9 (25.0)               | 38 (29.0)                | .18     |
| Hypertension                    | 50 (22.2)        | 14 (38.9)              | 35 (26.7)                | .09     |
| Diabetes                        | 37 (16.4)        | 6 (16.7)               | 29 (22.1)                | .39     |
| Liver cirrhosis                 | 4 (1.8)          | 0 (0.0)                | 3 (2.3)                  | .66     |
| Immune compromise               | 51 (22.7)        | 6 (16.7)               | 25 (19.1)                | .58     |
| Malignancy                      | 50 (22.2)        | 6 (16.7)               | 25 (19.1)                | .64     |
| Charlson comorbidity index      | 3 [1-5]          | 3 [2-5]                | 3 [2-5]                  | .86     |
| **Chronic medication**          |                  |                        |                          |         |
| Diuretics                       | 44 (19.6)        | 12 (33.3)              | 36 (27.5)                | .08     |
| ACE inhibitors / ARBs           | 46 (20.4)        | 9 (25.0)               | 38 (29.0)                | .18     |
| Calcium-entry blockers          | 29 (12.9)        | 8 (22.2)               | 18 (13.7)                | .32     |
| Beta-adrenergic blockers        | 52 (23.1)        | 10 (27.8)              | 44 (33.6)                | .10     |
| NSAIDs and Cox II inhibitors    | 34 (15.1)        | 8 (22.2)               | 13 (9.9)                 | .13     |
| Oral antidiabetic drugs         | 20 (8.9)         | 5 (13.9)               | 24 (18.3)                | .033    |
| Corticosteroids                 | 31 (13.8)        | 2 (5.6)                | 9 (6.9)                  | .07     |
| Antiplatelet drugs              | 46 (22.9)        | 7 (20.0)               | 38 (29.7)                | .29     |
| **Severity at time of admission to ICU** |                  |                        |                          |         |
| APACHE IV score                 | 71 [57-89]       | 83 [71-97]             | 91 [77-114]              | <.001   |
| Acute physiology score          | 59 [47-72]       | 70 [56-81]             | 79 [64-101]              | <.001   |
| mSOFA score                     | 6 [4-8]          | 8 [7-9]                | 10 [8-13]                | <.001   |
| Non-renal mSOFA score           | 6 [4-7]          | 7 [6-9]                | 8 [7-10]                 | <.001   |
| Shock                           | 91 (40.4)        | 25 (69.4)              | 109 (83.2)               | <.001   |
| ARDS                            | 63 (28.0)        | 11 (30.6)              | 50 (38.2)                | .14     |
| **Therapy during the first 24h**|                  |                        |                          |         |
| Mechanical ventilation          | 194 (86.2)       | 30 (83.3)              | 115 (87.8)               | .76     |
| Vasopressors                    | 130 (57.8)       | 29 (80.6)              | 118 (90.1)               | <.001   |
| Dose of vasopressors (mg)a      | 5.9 [2.3 - 14.4] | 15 [3.8 - 32.8]        | 18.4 [9.1 - 38.8]        | <.001   |
| Inotropes                       | 9 (4.0)          | 3 (8.3)                | 28 (21.4)                | <.001   |
| Dose of inotropes (mg)a         | 150.2 [75.5 - 344.8] | 218.3 [180.7 - 566.5] | 108.8 [51.5 - 256.9]     | .44     |
| RRT                             | 0 (0.0)          | 0 (0.0)                | 36 (27.5)†               | <.001   |
| Nephrotoxic drugs (≥ one)       | 115 (51.1)       | 20 (55.6)              | 105 (80.2)†              | <.001   |
| Aminoglycoside                  | 44 (19.6)        | 10 (27.8)              | 48 (36.6)†               | .002    |
| Glycopeptide                    | 25 (11.1)        | 4 (11.1)               | 14 (10.7)                | .99     |
| Colloid                         | 72 (32.0)        | 15 (41.7)              | 84 (64.1)                | <.001   |
| Other a                         | 11 (4.9)         | 2 (5.6)                | 8 (6.1)                  | .79     |
| Source of infection             |                  |                        |                          |         |
| Pulmonary tract                 | 130 (57.8)       | 17 (47.2)              | 48 (36.6)                | .001    |
| Abdominal                       | 42 (18.7)        | 11 (30.6)              | 43 (32.8)                | .007    |
| Cardiovascular                  | 23 (10.2)        | 2 (5.6)                | 17 (13.0)                | .47     |
| Urinary tract                   | 12 (5.3)         | 2 (5.6)                | 12 (9.2)                 | .37     |
| CNS                             | 8 (3.6)          | 0 (0.0)                | 1 (0.8)                  | .20     |
| Skin or soft tissue             | 8 (3.6)          | 2 (5.6)                | 9 (6.9)                  | .30     |
| Other b                         | 2 (0.9)          | 2 (5.6)                | 0 (0.0)                  | .05     |
| Unknown                         | 0 (0.0)          | 0 (0.0)                | 1 (0.8)                  | .43     |

*eTable 8 continued*
## Renal function during the first 24 hours

|                      | No AKI (n = 225) | Transient AKI (n = 36) | Persistent AKI (n = 131) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| Creatinine, µmol/L   | 80 [61-105]      | 136 [108-165]*         | 174 [136-240]†           | <.001   |
| Urea, mmol/L         | 7.1 [5.1-9.9]    | 11.3 [8.6-17.9]*       | 12.5 [8.9-17.8]*         | <.001   |
| Bicarbonate (minimal), mmol/L | 21.7 [18.2-26.2] | 19.3 [16.0-22.6]* | 16.2 [13.3-24.0]*† | <.001 |
| Urine output, mL     | 1780 [1265-2810] | 1595 [1068-2388]       | 965 [420-1413]*†         | <.001   |

### Outcome

|                      | No AKI (n = 225) | Transient AKI (n = 36) | Persistent AKI (n = 131) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| Duration of initial MV, days | 3 [1-7]        | 4 [2-8]                | 4 [2-10]                 | .09     |
| Recurrence of MV     | 7 (3.1)          | 4 (11.1)               | 8 (6.1)                  | .08     |
| MV-free days\(d\)   | 83 [39-88]       | 80 [25-88]             | 42 [2-82]†               | <.001   |
| Use of RRT           | 7 (3.1)          | 1 (2.8)                | 57 (43.5)†               | <.001   |
| RRT-free days\(d\)  | 90 [55-90]       | 90 [38-90]             | 57 [3-90]†               | <.001   |

### Complications\(e\)

|                      | No AKI (n = 225) | Transient AKI (n = 36) | Persistent AKI (n = 131) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| ICU length of stay, days | 5 [3-9]        | 7 [5-12]*              | 7 [3-13]*                | .002    |
| Hospital length of stay, days | 18 [10-36]   | 23 [14-41]             | 21 [6-45]†               | .38     |
| ICU-mortality         | 24 [10.7]       | 5 (13.9)               | 48 (36.6)†               | <.001   |
| 30-day mortality      | 45 [20.0]       | 8 (22.2)               | 59 (45.0)†               | <.001   |
| 60-day mortality      | 59 [26.2]       | 11 (30.6)              | 64 (48.9)†               | <.001   |
| 90-day mortality      | 65 [28.9]       | 11 (30.6)              | 69 (52.7)†               | <.001   |
| 1-year mortality      | 91 [40.4]       | 15 (41.7)              | 78 (59.5)†               | .002    |
| ICU-free days\(d\)   | 81 [39-87]      | 80 [15-84]             | 41 [8-81]†               | <.001   |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson \(\chi^2\) test or the Fisher’s exact test when appropriate. \(P\) value represent comparisons between the three groups.

\(\ast\) Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

\(\dagger\) Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

\(a\) Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

\(b\) Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

\(c\) Other sites of infection: Infections of bones and joints (n=1), Oral infections (n=1), Postoperative wound infections (n=1), Other (n=1).

\(d\) Between inclusion and day-90.

\(e\) Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
**eTable 9. Number and proportion of missing data among plasma biomarkers and white blood cell counts measured between admission and day 4**

|                                   | Admission | D2      | D4      |
|-----------------------------------|-----------|---------|---------|
| **No. At risk**                   | 866       | 713     | 487     |
| **Inflammatory response biomarkers** |           |         |         |
| IL-10                             | 0 (0 %)   | 49 (6.9 %) | 45 (9.2 %) |
| IL-6                              | 0 (0 %)   | 49 (6.9 %) | 45 (9.2 %) |
| IL-8                              | 0 (0 %)   | 49 (6.9 %) | 45 (9.2 %) |
| MMP8                              | 0 (0 %)   | 49 (6.9 %) | 44 (9 %)  |
| **WBC count**                     | 3 (0.3 %) | 25 (3.5 %) | 17 (3.5 %) |
| **Endothelial cell activation biomarkers** |           |         |         |
| Fractalkine                       | 1 (0.1 %) | 49 (6.9 %) | 49 (10.1 %) |
| sE-Selectin                       | 1 (0.1 %) | 49 (6.9 %) | 49 (10.1 %) |
| sICAM-1                           | 1 (0.1 %) | 49 (6.9 %) | 49 (10.1 %) |
| Angipoietin-1                     | 0 (0 %)   | 49 (6.9 %) | 44 (9 %)  |
| Angipoietin-2                     | 0 (0 %)   | 49 (6.9 %) | 44 (9 %)  |
| **Coagulation activation biomarkers** |           |         |         |
| D-dimer                           | 0 (0 %)   | 49 (6.9 %) | 44 (9 %)  |
| Protein C                         | 0 (0 %)   | 49 (6.9 %) | 44 (9 %)  |
| Antithrombin                      | 0 (0 %)   | 49 (6.9 %) | 44 (9 %)  |
| PT                                | 12 (1.4 %) | 65 (9.1 %) | 35 (7.2 %) |
| aPTT                              | 52 (6 %)  | 409 (57.4 %) | 316 (64.9 %) |
| Platelet count                    | 1 (0.1 %) | 25 (3.5 %) | 18 (3.7 %) |

Abbreviations: ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1; WBC, white blood cell.

Data presented as number (percentage among patients still present in the ICU).
Table 10. Baseline characteristics and outcomes of patients admitted with sepsis and still present in the intensive care unit on day 4, stratified according to the presence and evolution of acute kidney injury

|                         | No AKI (n = 543) | Transient AKI (n = 83) | Persistent AKI (n = 300) | P Value |
|-------------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**        |                  |                        |                          |         |
| Age, years              | 60 (48-70)       | 64 (49-73)             | 64 (53-72)               | .001    |
| Male sex                | 344 (63.4)       | 44 (53.0)              | 173 (57.7)               | .09     |
| Race, white             | 474 (87.6)       | 74 (89.2)              | 268 (89.9)               | .60     |
| Medical admission       | 420 (77.3)       | 60 (72.3)              | 216 (72.0)               | .18     |
| **Chronic comorbidities** |                |                        |                          |         |
| None                    | 155 (28.5)       | 25 (30.1)              | 73 (24.3)                | .35     |
| Cardiovascular comp      | 144 (26.5)       | 25 (30.1)              | 89 (29.7)                | .54     |
| Hypertension            | 142 (26.2)       | 26 (31.3)              | 85 (28.3)                | .54     |
| Diabetes                | 91 (16.8)        | 16 (19.3)              | 60 (20.0)                | .46     |
| Liver cirrhosis         | 5 (0.9)          | 4 (4.8)                | 11 (3.7)                 | .004    |
| Immune compromise        | 103 (19.0)       | 16 (19.3)              | 61 (20.3)                | .89     |
| Malignancy              | 113 (20.8)       | 14 (16.9)              | 80 (26.7)                | .07     |
| Charlson comorbidity index | 3 (1-4)        | 3 (2-5)                | 3 (2-5)                  | .003    |
| **Chronic medication**  |                  |                        |                          |         |
| Diuretics               | 114 (21.0)       | 21 (25.3)              | 78 (26.0)                | .21     |
| ACE inhibitors / ARBs   | 124 (22.8)       | 16 (19.3)              | 78 (26.0)                | .39     |
| Calcium-entry blockers  | 76 (14.0)        | 14 (16.9)              | 44 (14.7)                | .74     |
| Beta-adrenergic blockers| 118 (21.7)       | 21 (25.3)              | 82 (27.3)                | .18     |
| NSAIDs and Cox II inhibitors | 60 (11.0)     | 12 (14.5)              | 31 (10.3)                | .56     |
| Oral antidiabetic drugs | 66 (12.2)        | 11 (13.3)              | 45 (15.0)                | .49     |
| Corticosteroids         | 52 (9.6)         | 7 (8.4)                | 27 (9.0)                 | .96     |
| Antiplatelet drugs      | 122 (23.2)       | 18 (22.5)              | 68 (23.4)                | >.99    |
| **Severity at time of admission to ICU** |        |                        |                          |         |
| APACHE IV score         | 73 [59-91]       | 81 [67-96]*            | 97 [77-116]*†            | <.001   |
| Acute physiology score  | 61 [48-75]       | 69 [55-83]*            | 82 [66-102]*†            | <.001   |
| mSOFA score             | 6 [4-8]          | 8 [7-9]*               | 9 [8-12]*†               | <.001   |
| Non-renal mSOFA score   | 6 [4-7]          | 7 [6-8]*               | 8 [6-9]*                 | <.001   |
| Shock                   | 244 (44.9)       | 59 (71.1)*             | 238 (79.3)*              | <.001   |
| ARDS                    | 160 (29.5)       | 28 (33.7)              | 101 (33.7)               | .39     |
| **Therapy during the first 24h** |            |                        |                          |         |
| Mechanical ventilation  | 507 (93.4)       | 74 (89.2)              | 268 (89.3)               | .07     |
| Vasopressors            | 329 (60.6)       | 68 (81.9)*             | 264 (88.0)*              | <.001   |
| Dose of vasopressors (mg)a | 6.5 [2.3 - 14.7] | 12.5 [6.9 - 23.7]*     | 15.2 [6.4 - 31.8]*       | <.001   |
| Inotropes               | 26 (4.8)         | 9 (10.8)               | 57 (19.0)*               | <.001   |
| Dose of inotropes (mg)a | 154.4 [39.8 - 258.5] | 143.0 [49.1 - 332.3]  | 221.6 [83.9 - 356.9]    | .34     |
| RRT                     | 3 [0.6]          | 1 (1.2)                | 69 (23.1)*†              | <.001   |
| Nephrotoxic drugs (≥ one) | 216 (39.8)  | 46 (55.4)*             | 182 (60.7)*              | <.001   |
| Aminoglycoside          | 68 (12.5)        | 17 (20.5)              | 82 (27.3)*               | <.001   |
| Glycopeptide            | 64 (11.8)        | 11 (13.3)              | 51 (17.0)                | .11     |
| Colloid                 | 104 (19.2)       | 26 (31.3)*             | 109 (36.3)*              | <.001   |
| Other a                 | 51 (9.4)         | 8 (9.6)                | 29 (9.7)                 | .99     |
| **Source of infection** |                  |                        |                          |         |
| Pulmonary tract         | 361 (66.5)       | 44 (53.0)              | 111 (37.0)*†             | <.001   |
| Abdominal               | 58 (10.7)        | 20 (24.1)*             | 70 (23.3)*               | <.001   |
| Cardiovascular          | 38 (7.0)         | 4 (4.8)                | 42 (14.0)*               | .002    |
| Urinary tract           | 16 (2.9)         | 4 (4.8)                | 25 (8.3)*                | .002    |
| CNS                     | 27 (5.0)         | 2 (2.4)                | 10 (3.3)                 | .46     |
| Skin or soft tissue     | 14 (2.6)         | 3 (3.6)                | 19 (6.3)*                | .025    |
| Other c                 | 28 (5.2)         | 6 (7.2)                | 16 (5.3)                 | .68     |
| Unknown                 | 1 (0.2)          | 0 (0.0)                | 7 (2.3)*                 | .007    |

eTable 10 continued
| Renal function during the first 24 hours | No AKI (n = 543) | Transient AKI (n = 83) | Persistent AKI (n = 300) | P Value |
|----------------------------------------|-----------------|-----------------------|--------------------------|--------|
| Creatinine, µmol/L                     | 79 [61-103]     | 123 [91-154]*         | 174 [132-243]†           | <.001 |
| Urea, mmol/L                           | 6.9 [4.9-10.1]  | 10.5 [8.2-16.8]*      | 13.2 [9.1-18.8]*         | <.001 |
| Bicarbonate (minimal), mmol/L          | 22.5 [19.1-26.1] | 18.8 [16.7-22.6]*     | 16.8 [14.1-20.5]†        | <.001 |
| Urine output, mL                       | 1835 [1318-2718]| 1428 [961-2375]*      | 1028 [504-1620]*         | <.001 |

| Outcome | | | |
|---------| | | |
| Duration of initial MV, days           | 4 [2-8]         | 5 [2-8]                | 6 [3-11]*                | .015  |
| Recurrence of MV                       | 24 (4.4)        | 9 (10.8)               | 24 (8.0)                 | .020  |
| MV-free days\(d\)                      | 82 [30-87]      | 80 [24-87]             | 61 [2-83]†               | <.001 |
| Use of RRT                             | 22 (4.1)        | 4 (4.8)                | 131 (43.7)†              | <.001 |
| RRT-free days\(d\)                     | 90 [46-90]      | 90 [35-90]             | 73 [8-90]†               | <.001 |

| Complications<sup>a</sup> | | | |
|---------------------------| | | |
| None                      | 445 (82.0)      | 69 (83.1)              | 232 (77.3)               | .23   |
| ICU-acquired AKI           | 57 (10.5)       | 4 (4.8)                | 12 (4.0)*                | .002  |
| ICU-acquired ARDS          | 20 (3.7)        | 3 (3.6)                | 10 (3.3)                 | .96   |
| ICU-acquired infection     | 47 (8.7)        | 10 (12.0)              | 56 (18.7)*               | <.001 |
| ICU length of stay, days   | 7 [5-11]        | 8 [5-12]               | 9 [5-16]                 | .002  |
| Hospital length of stay, days | 19 [11-36]  | 21 [12-35]             | 24 [11-41]               | .33   |
| ICU-mortality              | 75 (13.8)       | 13 (15.7)              | 95 (31.7)*               | <.001 |
| 30-day mortality           | 120 (22.1)      | 19 (22.9)              | 108 (36.0)*              | <.001 |
| 60-day mortality           | 151 (27.8)      | 25 (30.1)              | 133 (44.3)*              | <.001 |
| 90-day mortality           | 165 (30.4)      | 27 (32.5)              | 146 (48.7)†              | <.001 |
| 1-year mortality           | 211 (38.9)      | 35 (42.2)              | 169 (56.3)*              | <.001 |
| ICU-free days<sup>d</sup>  | 79 [32-84]      | 79 [19-84]             | 61 [0-81]†               | <.001 |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson \( \chi^2 \) test or the Fisher’s exact test when appropriate. \( P \) value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

<sup>a</sup> Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

<sup>b</sup> Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

<sup>c</sup> Infections of bones and joints (n=6), Oral infections (n=6), Postoperative wound infections (n=11), Upper respiratory tract infections (n=9), Viral systemic infections (n=4), Other (n=14).

<sup>d</sup> Between inclusion and day-90.

<sup>e</sup> Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### eTable 11. Logistic regression analysis evaluating the influence of the evolution of acute kidney injury on 30-day and 1-year mortality in patients still present in the ICU on day 4

|                      | 30-day mortality | 1-year mortality |
|----------------------|------------------|------------------|
|                      | Odds Ratio       | P Value          | Wald test χ² (df), P | Odds Ratio       | P Value          | Wald test χ² (df), P |
|                      | (95% CI)         |                  |                      | (95% CI)         |                  |                      |
| **Crude model**      |                  |                  |                      |                  |                  |                      |
| No AKI               | 1.00 (reference) | -                | 19.4 (2), <.001      | 1.00 (reference) | -                | 23.8 (2), <.001    |
| Transient AKI        | 1.05 (0.60-1.82) | .87              | 1.15 (0.72-1.83), .57 | 1.15 (0.72-1.83) | .57              |
| Persistent AKI       | 1.98 (1.45-2.71) | <.001            | 2.03 (1.52-2.70), <.001 | 2.03 (1.52-2.70) | <.001            |
| **Adjusted model**   |                  |                  |                      |                  |                  |                      |
| No AKI               | 1.00 (reference) | -                | 5.76 (2), .056       | 1.00 (reference) | -                | 5.64 (2), .021     |
| Transient AKI        | 1.65 (0.74-3.66) | .22              | 1.55 (0.73-3.29), .26 | 1.55 (0.73-3.29) | .26              |
| Persistent AKI       | 2.24 (1.15-4.34) | .018             | 2.16 (1.12-4.17), .021 | 2.16 (1.12-4.17) | .021             |

- **Crude model**
- **Adjusted model**

Unadjusted model.

Adjusted for age, admission RIFLE score, APACHE acute physiology score, source of infection, and modified-Charlson comorbidity index (omitting the age parameter).
eTable 12. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis and with plasma biomarkers measured upon admission, stratified according to the presence and evolution of acute kidney injury after propensity matching

|                        | No AKI (n = 162) | Transient AKI (n = 54) | Persistent AKI (n = 116) | P Value |
|------------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**       |                  |                        |                          |         |
| Age, years             | 64 [56-74]       | 67 [54-72]             | 64 [54-72]               | .63     |
| Male sex               | 88 (54.3)        | 30 (55.6)              | 63 (54.3)                | >.99    |
| Race, white            | 139 (86.3)       | 46 (85.2)              | 103 (90.4)               | .51     |
| Medical admission      | 120 (74.1)       | 39 (72.2)              | 83 (71.6)                | .89     |
| **Chronic comorbidities** |                |                        |                          |         |
| None                   | 36 (22.2)        | 14 (25.9)              | 33 (28.4)                | .49     |
| Cardiovascular compromise | 48 (29.6)       | 17 (31.5)              | 36 (31.0)                | .96     |
| Hypertension           | 48 (29.6)        | 24 (44.4)              | 33 (28.4)                | .09     |
| Diabetes               | 34 (21.0)        | 11 (20.4)              | 24 (20.7)                | >.99    |
| Liver cirrhosis        | 5 (3.1)          | 1 (1.9)                | 0 (0.0)                  | .15     |
| Immune compromise      | 37 (22.8)        | 7 (13.0)               | 26 (22.4)                | .29     |
| Malignancy             | 46 (28.4)        | 8 (14.8)               | 31 (26.7)                | .13     |
| Charlson comorbidity index | 4 [2-6]        | 3 [2-5]                | 3 [2-5]                  | .48     |
| **Chronic medication** |                  |                        |                          |         |
| Diuretics              | 39 (24.1)        | 14 (25.9)              | 30 (25.9)                | .93     |
| ACE inhibitors / ARBs  | 42 (25.9)        | 12 (22.2)              | 27 (23.3)                | .86     |
| Calcium-entry blockers | 24 (14.8)        | 10 (18.5)              | 20 (17.2)                | .73     |
| Beta-adrenergic blockers | 43 (26.5)       | 12 (22.2)              | 31 (26.7)                | .82     |
| NSAIDs and Cox II inhibitors | 18 (11.1) | 9 (16.7)               | 18 (15.5)                | .40     |
| Oral antidiabetic drugs | 24 (14.8)       | 8 (14.8)               | 18 (15.5)                | .98     |
| Corticosteroids        | 23 (14.2)        | 3 (5.6)                | 14 (12.1)                | .25     |
| Antiplatelet drugs     | 42 (27.8)        | 10 (18.9)              | 31 (27.9)                | .43     |
| **Severity at time of admission to ICU** | | | | |
| APACHE IV score        | 83 [67-97]       | 81 [66-96]             | 81 [67-97]               | .86     |
| Acute physiology score | 68 [54-79]       | 69 [55-79]             | 68 [56-81]               | .89     |
| mSOFA score            | 7 [6-8]          | 8 [6-9]*               | 8 [7-10]*                | <.001   |
| Non-renal mSOFA score | 7 [5-8]          | 7 [6-8]                | 7 [5-8]                  | .62     |
| Shock                  | 92 (56.8)        | 37 (68.5)              | 76 (65.5)                | .18     |
| ARDS                   | 63 (38.9)        | 19 (35.2)              | 42 (36.2)                | .89     |
| **Therapy during the first 24h** | | | | |
| Mechanical ventilation | 149 (92.0)       | 48 (88.9)              | 94 (81.0)*               | .026    |
| Vasopressors           | 120 (74.1)       | 41 (75.9)              | 87 (75.0)                | .97     |
| Dose of vasopressors (mg)* | 8.7 [3.1 - 15.5] | 12.8 [5.1 - 21.2] | 12.2 [5.0 - 24.2]*       | .032    |
| Inotropes              | 8 (4.9)          | 3 (5.6)                | 13 (11.2)                | .16     |
| Dose of inotropes (mg)* | 151.4 [26.3 - 349.2] | 218.3 [180.7 - 566.5] | 225.5 [190.6 - 356.9] | .62     |
| RRT                    | 2 (1.2)          | 3 (5.6)                | 18 (15.7)*               | <.001   |
| Nephrotic drugs (≥ one) | 80 (49.4)        | 28 (51.9)              | 70 (60.3)                | .18     |
| Aminoglycoside         | 39 (24.1)        | 13 (24.1)              | 24 (20.7)                | .77     |
| Glycopeptide           | 21 (13.0)        | 3 (5.6)                | 21 (18.1)                | .08     |
| Colloid                | 41 (25.3)        | 19 (35.2)              | 40 (34.5)                | .16     |
| Other*                | 16 (9.9)         | 3 (5.6)                | 14 (12.1)                | .45     |
| **Source of infection** |                  |                        |                          |         |
| Pulmonary tract        | 83 (51.2)        | 27 (50.0)              | 51 (44.0)                | .48     |
| Abdominal              | 39 (24.1)        | 14 (25.9)              | 35 (30.2)                | .52     |
| Cardiovascular         | 9 (5.6)          | 4 (7.4)                | 6 (5.2)                  | .86     |
| Urinary tract          | 12 (7.4)         | 3 (5.6)                | 7 (6.0)                  | .92     |
| CNS                    | 6 (3.7)          | 1 (1.9)                | 5 (4.3)                  | .86     |
| Skin or soft tissue    | 7 (4.3)          | 3 (5.6)                | 8 (6.9)                  | .61     |
| Other*                | 6 (3.7)          | 2 (3.7)                | 3 (2.6)                  | .85     |
| Unknown                | 0 (0.0)          | 0 (0.0)                | 1 (0.9)                  | .51     |

*eTable 12 continued*
### Renal function during the first 24 hours

|                      | No AKI (n = 162) | Transient AKI (n = 54) | Persistent AKI (n = 116) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| Creatinine, µmol/L   | 84 [65-115]      | 135 [92-163]*         | 175 [113-227]*           | <.001   |
| Urea, mmol/L         | 8.6 [6.3-11.6]   | 10.8 [8.3-18.6]*      | 13.5 [9.4-17.7]*         | <.001   |
| Bicarbonate (minimal), mmol/L | 21.5 [18.3-25.2] | 19.3 [16.9-22.9]* | 17.7 [15.7-21.1]* | <.001 |
| Urine output, mL     | 1755 [1329-2625] | 1595 [980-2380]       | 1173 [734-2130]*         | <.001   |

### Outcome

|                      | No AKI (n = 162) | Transient AKI (n = 54) | Persistent AKI (n = 116) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| Duration of initial MV, days | 3 [2-7] | 5 [2-7] | 3 [1-9] | .44 |
| Recurrence of MV | 6 (3.7) | 5 (9.3) | 5 (4.3) | .25 |
| MV-free days$^d$  | 81 [7-88] | 81 [32-88] | 78 [9-88] | .64 |
| Use of RRT   | 11 (6.8) | 4 (7.4) | 35 (30.2)$^†$ | <.001 |
| RRT-free days$^d$ | 90 [16-90] | 90 [42-90] | 88 [17-90]$^†$ | .027 |

### Complications$^a$

|                      | No AKI (n = 162) | Transient AKI (n = 54) | Persistent AKI (n = 116) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| None                 | 136 (84.0)       | 46 (85.2)              | 97 (83.6)                | >.99    |
| ICU-acquired AKI     | 16 (9.9)         | 3 (5.6)                | 6 (5.2)                  | .34     |
| ICU-acquired ARDS    | 6 (3.7)          | 1 (1.9)                | 4 (3.4)                  | .92     |
| ICU-acquired infection | 12 (7.4)    | 6 (11.1)               | 15 (12.9)                | .29     |
| ICU length of stay, days | 5 [3-10] | 8 [5-12] | 6 [3-12] | .07 |
| Hospital length of stay, days | 16 [9-33] | 20 [12-40] | 19 [11-40] | .39 |
| ICU-mortality        | 33 (20.4)        | 6 (11.1)               | 28 (24.1)                | .13     |
| 30-day mortality     | 46 (28.4)        | 11 (20.4)              | 32 (27.6)                | .53     |
| 60-day mortality     | 56 (34.6)        | 15 (27.8)              | 43 (37.1)                | .50     |
| 90-day mortality     | 61 (37.7)        | 16 (29.6)              | 47 (40.5)                | .39     |
| 1-year mortality     | 78 (48.1)        | 22 (40.7)              | 59 (50.9)                | .49     |
| ICU-free days$^d$    | 79 [7-86]        | 81 [39-85]             | 76 [4-85]                | .72     |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Using a propensity score, patient groups were matched for age, sex, modified Charlson comorbidity index (excluding age), APACHE acute physiology score, non-renalin mSOFA score and for the site of infection.

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher's exact test when appropriate. P value represent comparisons between the three groups.

$^*$ Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

$^†$ Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

$^a$ Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

$^b$ Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

$^c$ Other sites of infection: Infections of bones and joints (n=4), Oral infections (n=2), Postoperative wound infections (n=1), Upper respiratory tract infections (n=2), Viral systemic infections (n=2).

$^d$ Between inclusion and day-90.

$^e$ Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### eTable 13. Host response biomarkers in patients with sepsis during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission, in the propensity matched cohort

|                       | Admission | Day-2 | Day 4 |
|-----------------------|-----------|-------|-------|
|                       | No AKI (n=162) | Transient AKI (n=54) | Persistent AKI (n=116) | No AKI (n=137) | Transient AKI (n=54) | Persistent AKI (n=86) | No AKI (n=87) | Transient AKI (n=37) | Persistent AKI (n=66) | P Value (group) | P Value (time x group) |
| **Inflammatory responses** |           |       |       |           |       |       |           |       |       |       |           |           |
| IL-10 (pg/mL)         | 9.8       | 19.6  | 26.3  | 7.3       | 7.6   | 12.9  | 5.1       | 4.5   | 9.0   | <.001   | .031       |           |
|                       | [3.7-29.7] | [7.9-49.8]* | [8.5-108.0]* | [3.2-14.0] | [3.7-14.4] | [4.3-42.1]* | [2.4-11.4] | [2.8-6.9] | [3.5-31.4]*† † |           |           |
| IL-6 (pg/mL)          | 184.3     | 288.2 | 408.7 | 76.3      | 103.7 | 86.1  | 47.3      | 26.4  | 50.2  | .19      | .049       |           |
|                       | [43.6-921.9] | [75.0-1403.7] | [2063.3] | [21.2-245.0] | [197.8] | [370.0] | [13.5-168.8] | [11.1-75.0] | [15.9-99.0] |           |           |
| IL-8 (pg/mL)          | 107.4     | 158.1 | 185.6 | 62.9      | 86.2  | 127.2 | 51.1      | 57.5  | 90.5  | .001     | .20        |           |
|                       | [37.7-346.4] | [71.4-567.6] | [760.8]* | [28.1-149.9] | [172.6] | [372.9]*† | [23.4-134.5] | [31.5-72.7] | [43.8-215.2]*† |           |           |
| MMP-8 (ng/mL)         | 2.6       | 7.0   | 5.6   | 1.7       | 2.7   | 2.5   | 1.2       | 1.3   | 2.1   | .001     | .10        |           |
|                       | [0.9-7.7] | [2.4-16.2]* | [1.9-15.5]* | [0.5-5.2] | [1.2-8.8] | [1.0-8.2] | [0.4-3.6] | [0.7-3.6] | [1.2-6.1]* |           |           |
| **Endothelial cell activation** |           |       |       |           |       |       |           |       |       |           |           |           |
| Fractalkine (pg/mL)   | 22.2      | 32.3  | 32.0  | 19.7      | 29.5  | 34.3  | 21.7      | 27.3  | 44.2  | .005     | .043       |           |
|                       | [13.4-53.8] | [14.7-67.3] | [17.3-83.1]* | [12.8-40.1] | [12.8-61.4] | [15.8-80.2]* | [13.4-73.6] | [15.3-55.6] | [28.5-93.7]* |           |           |
| sE-Selectin (ng/mL)   | 8.6       | 12.3  | 13.0  | 10.0      | 10.0  | 9.7   | 9.2       | 9.4   | 8.6   | .32       | .08        |           |
|                       | [4.4-21.4] | [5.0-32.3] | [5.4-26.8] | [4.1-17.9] | [4.4-22.4] | [3.9-19.5] | [3.4-19.3] | [4.0-15.3] | [4.2-16.4] |           |           |
| sICAM-1 (ng/mL)       | 184.4     | 148.2 | 1976  | 205.8     | 168.3 | 218.6 | 241.9     | 169.6 | 247.1 | .29       | .56        |           |
|                       | [96.9-320.6] | [93.1-277.0] | [310.5] | [109.9-338.7] | [299.4] | [355.4] | [146.2-363.5] | [111.9-326.1] | [162.9-376.6] |           |           |
| Angiopoietin-1 (ng/mL)| 2.6       | 3.4   | 2.5   | 1.9       | 2.0   | 1.1   | 1.7       | 2.1   | 1.1   | .13       | .11        |           |
|                       | [0.9-6.6] | [1.1-8.6] | [1.0-5.5] | [0.8-4.9] | [0.9-3.9] | [0.6-2.9]* | [0.7-4.3] | [1.1-4.8] | [0.5-3.0]*† |           |           |
| Angiopoietin-2 (ng/mL)| 7.3       | 7.8   | 10.0  | 6.8       | 9.4   | 12.0  | 6.8       | 5.4   | 7.9   | .18       | .68        |           |
|                       | [2.8-13.1] | [3.2-15.9] | [4.5-22.7]* | [3.7-14.5] | [3.8-19.9] | [4.6-26.7]* | [3.2-12.0] | [3.4-8.0] | [4.1-15.2]*† |           |           |
| ANG-2:ANG-1 (ng/mL)   | 2.2       | 2.2   | 4.5   | 3.6       | 4.3   | 9.5   | 3.5       | 2.6   | 7.8   | .07       | .69        |           |
|                       | [0.6-9.2] | [0.7-7.2] | [0.9-19.3] | [1.1-12.0] | [1.7-15.5] | [2.7-28.4]* | [0.9-10.8] | [0.7-6.0]* | [2.5-20.4]* |           |           |
### eTable 13 continued

| Coagulation activation | Admission | Day-2 | Day 4 | P Value (group) | P Value (time x group) |
|------------------------|-----------|-------|-------|-----------------|------------------------|
|                        | No AKI (n=162) | Transient AKI (n=54) | Persistent AKI (n=116) | No AKI (n=137) | Transient AKI (n=54) | Persistent AKI (n=86) | No AKI (n=87) | Transient AKI (n=37) | Persistent AKI (n=66) |
| D-dimer (µg/mL)        | 9.3 [4.7-17.5] | 8.4 [3.8-14.7] | 12.1 [6.8-21.9]| 8.9 [3.8-15.1] | 9.6 [3.8-14.8] | 11.9 [5.8-19.9]| 10.2 [5.6-18.3] | 6.4 [4.4-14.3] | 13.2 [8.5-22.0] |
| Protein C (ng/mL)     | 108.4 [83.8-139.8] | 93.1 [77.7-150.9] | 110.8 [87.1-148.3] | 113.6 [84.2-148.0] | 95.7 [70.5-122.9] | 116.7 [81.2-155.3] | 125.6 [83.1-162.2] | 129.1 [82.4-156.9] | 128.0 [96.2-173.8] |
| Anti-thrombin (ng/mL) | 673.7 [495.4-1020.7] | 649.2 [467.3-970.7] | 644.3 [437.9-1043.2] | 722.7 [446.0-951.2] | 699.3 [420.5-1047.3] | 657.2 [466.5-962.1] | 702.4 [528.1-1352.8] | 936.8 [618.6-1609.4] | 879.9 [629.3-1388.5] |
| PT (sec)               | 15.3 [13.1-18.0] | 14.1 [12.4-18.0] | 15.6 [13.4-18.6] | 15.0 [12.0-17.0] | 13.0 [11.0-16.0] | 14.5 [13.0-17.0] | 14.0 [12.2-16.0] | 13.0 [11.0-15.0] | 14.0 [12.0-16.5] |
| aPTT (sec)             | 36.0 [30.0-47.2] | 34.0 [29.2-39.0] | 39.0 [32.0-51.5] | 35.0 [30.0-44.8] | 33.0 [30.0-37.5] | 40.0 [32.5-47.0] | 32.0 [26.5-43.0] | 30.0 [27.0-35.0] | 40.0 [31.0-49.0] |
| Platelets (10^9/L)     | 178.0 [106.0-266.0] | 167.0 [113.2-238.5] | 158.0 [83.2-247.5] | 170.0 [81.0-257.5] | 144.0 [93.0-203.0] | 146.0 [83.0-228.0] | 164.0 [87.0-253.0] | 168.0 [80.8-226.0] | 128.5 [53.5-194.5] |

Abbreviations: ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Data presented as median [interquartile range]

Using a propensity score, patient groups were matched for age, sex, modified Charlson comorbidity index (excluding age), APACHE acute physiology score, non-renal mSOFA score and for the site of infection.

Overall P values are derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn's post hoc tests of multiple comparisons using rank sums.

* Significant vs no AKI
† Significant vs Transient AKI
**Table 14. Baseline characteristics and outcomes of patients admitted to the ICU with septic shock, stratified according to the presence and evolution of acute kidney injury**

| Demographics | No AKI (n = 362) | Transient AKI (n = 73) | Persistent AKI (n = 349) | P Value |
|--------------|-----------------|------------------------|--------------------------|---------|
| Age, years   | 62 [51 - 71]    | 62 [49 - 73]           | 66 [56 - 74]             | .002    |
| Male sex     | 224 (61.9)      | 43 (58.9)              | 202 (57.9)               | .54     |
| Race, white  | 321 (89.4)      | 64 (87.7)              | 308 (89.5)               | .87     |
| Medical admission | 244 (67.4) | 50 (68.5)              | 239 (68.5)               | .96     |
| Chronic comorbidities |              |                        |                          |         |
| None         | 106 (29.3)      | 18 (24.7)              | 100 (28.7)               | .74     |
| Cardiovascular compromise | 105 (29.0) | 28 (38.4)              | 99 (28.4)                | .23     |
| Hypertension | 99 (27.3)       | 29 (39.7)              | 101 (28.9)               | .11     |
| Diabetes     | 61 (16.9)       | 17 (23.3)              | 68 (19.5)                | .36     |
| Liver cirrhosis | 5 (1.4)     | 3 (4.1)                | 9 (2.6)                  | .19     |
| Immune compromise | 70 (19.3)  | 12 (16.4)              | 69 (19.8)                | .85     |
| Malignancy   | 77 (21.3)       | 13 (17.8)              | 84 (24.1)                | .45     |
| Charlson comorbidity index | 3 [1 - 5]   | 3 [2 - 5]              | 3 [2 - 5]                | .06     |
| Chronic medication |            |                        |                          |         |
| Diuretics    | 79 (21.8)       | 20 (27.4)              | 94 (26.9)                | .24     |
| ACE inhibitors / ARBs | 97 (26.8) | 18 (24.7)              | 96 (27.5)                | .90     |
| Calcium-entry blockers | 51 (14.1) | 12 (16.4)              | 49 (14.0)                | .84     |
| Beta-adrenergic blockers | 91 (25.1) | 24 (32.9)              | 95 (27.2)                | .37     |
| NSAIDs and Cox II inhibitors | 40 (11.0)  | 10 (13.7)              | 41 (11.7)                | .76     |
| Oral antidiabetic drugs | 41 (11.3) | 13 (17.8)              | 51 (14.6)                | .21     |
| Corticosteroids | 39 (10.8)  | 6 (8.2)                | 31 (8.9)                 | .67     |
| Antiplatelet drugs | 91 (26.2) | 17 (23.9)              | 85 (25.1)                | .92     |
| Severity at time of admission to ICU |              |                        |                          |         |
| APACHE IV score | 75 [61 - 93] | 77 [66 - 93]           | 101 [81 - 124]††        | <.001   |
| Acute physiology score | 64 [50 - 79] | 65 [55 - 80]           | 87 [67 - 109]††         | <.001   |
| mSOFA score   | 7 [6 - 9]       | 8 [7 - 10]*            | 10 [8 - 12]††           | <.001   |
| Non-renal mSOFA score | 7 [6 - 8] | 7 [6 - 8]              | 8 [7 - 10]††            | <.001   |
| Shock          | 362 (100.0)     | 73 (100.0)             | 349 (100.0)              | >.99    |
| ARDS          | 106 (29.3)      | 19 (26.0)              | 114 (32.7)               | .44     |
| Therapy during the first 24h |              |                        |                          |         |
| Mechanical ventilation | 341 (94.2) | 66 (90.4)              | 317 (90.8)               | .18     |
| Vasopressors  | 362 (100.0)     | 73 (100.0)             | 349 (100.0)              | >.99    |
| Dose of vasopressors (mg) | 9.4 [4.2 - 16.3] | 12.5 [6.3 - 23.6]* | 18.2 [8.5 - 37.1]*††   | <.001   |
| Inotropes     | 32 (8.8)        | 9 (12.3)               | 80 (22.9)*               | <.001   |
| Dose of inotropes (mg) | 141.6 [26.8 - 254.7] | 109.8 [49.1 - 218.3] | 179.4 [63.9 - 319.4] | .32     |
| RRT           | 5 (1.4)         | 3 (4.1)                | 86 (24.7)*               | <.001   |
| Nephrotoxic drugs (≥ one) | 167 (46.1) | 44 (60.3)*             | 227 (65.0)*              | <.001   |
| Aminoglycoside | 59 (16.3)       | 18 (24.7)              | 113 (32.4)*              | <.001   |
| Glycopeptide  | 49 (13.5)       | 9 (12.3)               | 67 (19.2)                | .09     |
| Colloid       | 95 (26.2)       | 29 (39.7)              | 154 (44.1)*              | <.001   |
| Other*        | 25 (6.9)        | 6 (8.2)                | 21 (6.0)                 | .67     |
| Source of infection |              |                        |                          |         |
| Pulmonary tract | 212 (58.6) | 35 (47.9)              | 117 (33.5)*              | <.001   |
| Abdominal     | 57 (15.7)       | 22 (30.1)*             | 108 (30.9)*              | <.001   |
| Cardiovascular | 28 (7.7)        | 4 (5.5)                | 44 (12.6)                | .043    |
| Urinary tract | 16 (4.4)        | 3 (4.1)                | 31 (8.9)                 | .047    |
| CNS           | 14 (3.9)        | 2 (2.7)                | 6 (1.7)                  | .19     |
| Skin or soft tissue | 15 (4.1)    | 4 (5.5)                | 21 (6.0)                 | .50     |
| Other*        | 20 (5.5)        | 3 (4.1)                | 15 (4.3)                 | .73     |
| Unknown       | 0 (0.0)         | 0 (0.0)                | 7 (2.0)*                 | .011    |
### eTable 14 continued

|                          | No AKI (n = 209) | Transient AKI (n = 42) | Persistent AKI (n = 233) | P Value |
|--------------------------|------------------|------------------------|--------------------------|--------|
| **Hemodynamic variables and renal function during the first 24 hours** |                  |                        |                          |        |
| ABPm (minimum), mmHg     | 56 [50 - 60]     | 56 [50 - 60]           | 53 [48 - 59]*†          | <.001  |
| CVP, mmHg                | 11 [7 - 14]      | 11 [8 - 16]            | 14 [10 - 18]*†          | <.001  |
| Creatinine, µmol/L       | 85 [66 - 114]    | 141 [97 - 171]*       | 174 [136 - 239]*†       | <.001  |
| Urea, mmol/L             | 7.2 [5.4 - 10.3] | 11.2 [8.4 - 17.8]*    | 13.0 [9.4 - 18.8]*      | <.001  |
| Bicarbonate (minimal), mmol/L | 20.9 [17.5 - 24.0] | 18.7 [16.3 - 22.0]* | 15.5 [12.6 - 18.6]*    | <.001  |
| Urine output, mL         | 1780 [1225 - 2790] | 1515 [1055 - 2440]   | 800 [340 - 1375]*†      | <.001  |
| **Outcome**              |                  |                        |                          |        |
| Duration of initial MV, days | 3 [2 - 7]       | 3 [2 - 7]            | 3 [2 - 9]               | .85    |
| Recurrence of MV         | 11 (3.0)         | 8 (11.0)*             | 20 (5.7)                | .012   |
| MV-free daysd            | 83 [18 - 88]     | 84 [31 - 88]          | 15 [1 - 83]*†           | <.001  |
| Use of RRT               | 18 (5.0)         | 4 (5.5)               | 140 [40.1]*†            | <.001  |
| RRT-free daysd           | 90 [36 - 90]     | 90 [46 - 90]          | 31 [2 - 90]*†           | <.001  |
| **Complicationsa**       |                  |                        |                          |        |
| None                     | 316 (87.3)       | 62 (84.9)             | 289 (82.8)              | .24    |
| ICU-acquired AKI         | 27 (7.5)         | 3 (4.1)               | 10 (2.9)*               | .017   |
| ICU-acquired ARDS        | 10 (2.8)         | 3 (4.1)               | 10 (2.9)                | .70    |
| ICU-acquired infection   | 27 (7.5)         | 8 (11.0)              | 50 (14.3)*              | .013   |
| ICU length of stay, days | 5 [3 - 10]       | 6 [4 - 10]            | 6 [3 - 12]              | .10    |
| Hospital length of stay, days | 17 [9 - 36]     | 20 [12 - 38]          | 15 [4 - 36]*†           | .006   |
| ICU-mortality            | 61 (16.9)        | 9 (12.3)              | 157 (45.0)*†            | <.001  |
| 30-day mortality         | 87 (24.0)        | 14 (19.2)             | 166 (47.6)*†            | <.001  |
| 60-day mortality         | 105 (29.0)       | 19 (26.0)             | 188 (53.9)*†            | <.001  |
| 90-day mortality         | 117 (32.3)       | 20 (27.4)             | 199 (57.0)*†            | <.001  |
| 1-year mortality         | 158 (43.6)       | 27 (37.0)             | 225 (64.5)*†            | <.001  |
| ICU-free daysd           | 80 [19 - 86]     | 81 [37 - 86]          | 12 [0 - 60]*†           | <.001  |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

a Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

Other nephrotoxic drug includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

Other sites of infection: Infections of bones and joints (n= 8), Postoperative wound infections (n= 11), Upper respiratory tract infections (n= 4), Viral systemic infections (n= 3), other (n= 12).

Between inclusion and day-90.

* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
**etTable 15. Baseline characteristics and outcomes of patients admitted to the ICU with a septic shock, stratified according to treatment with dobutamine.**

|                               | No dobutamine (n = 663) | Dobutamine (n = 121) | P value |
|--------------------------------|-------------------------|----------------------|---------|
| **Demographics**               |                         |                      |         |
| Age, years                     | 63 [52 - 72]            | 66 [56 - 73]         | .044    |
| Male sex                       | 390 (58.8)              | 79 (65.3)            | .19     |
| Race, white                    | 586 (89.2)              | 107 (89.9)           | >.99    |
| Medical admission              | 460 (69.4)              | 73 (60.3)            | .06     |
| **Chronic comorbidities**      |                         |                      |         |
| None                           | 197 (29.7)              | 27 (22.3)            | .10     |
| Cardiovascular compromise      | 172 (25.9)              | 60 (49.6)            | <.001   |
| Hypertension                   | 194 (29.3)              | 35 (28.9)            | >.99    |
| Diabetes                       | 126 (19.0)              | 20 (16.5)            | .61     |
| Liver cirrhosis                | 16 (2.4)                | 1 (0.8)              | .49     |
| Immune compromise              | 128 (19.3)              | 23 (19.0)            | >.99    |
| Malignancy                     | 156 (23.5)              | 18 (14.9)            | .043    |
| Charlson comorbidity index     | 3 [2 - 5]               | 3 [2 - 5]            | .41     |
| **Chronic medication**         |                         |                      |         |
| Diuretics                      | 165 (24.9)              | 28 (23.1)            | .73     |
| ACE inhibitors / ARBs          | 167 (25.2)              | 44 (36.4)            | .014    |
| Calcium-entry blockers         | 99 (14.9)               | 13 (10.7)            | <.001   |
| Beta-adrenergic blockers       | 168 (25.3)              | 42 (34.7)            | .035    |
| NSAIDs and Cox II inhibitors   | 79 (11.9)               | 12 (9.9)             | .64     |
| Oral anti-diabetic drugs       | 90 (13.6)               | 15 (12.4)            | .89     |
| Corticosteroids                | 65 (9.8)                | 11 (9.1)             | >.99    |
| Antiplatelet drugs             | 155 (23.4)              | 38 (32.2)            | .08     |
| **Severity at time of admission to ICU** |                         |                      |         |
| APACHE IV score                | 84 [67 - 108]           | 97 [74 - 123]        | <.001   |
| Acute physiology score         | 71 [56 - 93]            | 85 [63 - 105]        | <.001   |
| mSOFA score                    | 8 [7 - 10]              | 10 [8 - 12]          | <.001   |
| Non-renal mSOFA score          | 7 [6 - 9]               | 8 [7 - 9]            | .002    |
| Shock                          | 663 (100.0)             | 121 (100.0)          | >.99    |
| ARDS                           | 207 (31.2)              | 32 (26.4)            | .33     |
| **Physiological variables and therapy during the first 24 hours** |                         |                      |         |
| Mechanical ventilation         | 610 (92.0)              | 114 (94.2)           | .46     |
| Vasopressors                   | 663 (100.0)             | 121 (100.0)          | >.99    |
| Dose of vasopressors (mg)a     | 11.6 [5.2 - 21.3]       | 19.6 [11.8 - 42.7]   | <.001   |
| Dose of inotropes (mg)a        | NA                      | 152.4 [57.5 - 305.7] | NA      |
| RRT                            | 67 (10.1)               | 27 (22.3)            | <.001   |
| Nephrotoxic drugs (≥ one)      | 365 (55.1)              | 73 (60.3)            | .32     |
| Aminoglycoside                 | 159 (24.0)              | 31 (25.6)            | .73     |
| Glycopeptide                   | 104 (15.7)              | 21 (17.4)            | .69     |
| Colloid                        | 227 (34.2)              | 51 (42.1)            | .10     |
| Otherc                         | 44 (6.6)                | 8 (6.6)              | >.99    |
| **Source of infection**        |                         |                      |         |
| Pulmonary tract                | 315 (47.5)              | 49 (40.5)            | .17     |
| Abdominal sepsis               | 163 (24.6)              | 24 (19.8)            | .30     |
| Cardiovascular                 | 50 (7.5)                | 26 (21.5)            | <.001   |
| Urinary tract                  | 40 (6.0)                | 10 (8.3)             | .42     |
| CNS                            | 22 (3.3)                | 0 (0.0)              | .036    |
| Skin or soft tissue            | 34 (5.1)                | 6 (5.0)              | >.99    |
| Otherc                         | 34 (5.1)                | 4 (3.3)              | .50     |
| Unknown                        | 5 (0.8)                 | 2 (1.7)              | .30     |
| No dobutamine (n= 663) | Dobutamine (n= 121) | P value |
|------------------------|---------------------|---------|
| Hemodynamic variables and renal function during the first 24 hours | | |
| ABPm (lowest), mmHg | 55 [50 - 60] | 52 [47 - 58] | .01 |
| CVP, mmHg | 12 [8 - 16] | 14 [9.8 - 19.3] | .01 |
| Creatinine (µmol/L) | 116 [79 - 170] | 157 [108 - 206] | <.01 |
| Urea (mmol/L) | 9.9 [6.6 - 14.4] | 12.10 [8.20 - 17.40] | .006 |
| Bicarbonate (min), mmol/L | 18.6 [15.0 - 22.3] | 16.90 [12.60 - 20.50] | <.01 |
| Urine output, mL | 1380 [833 - 2330] | 1005 [405 - 1745] | <.01 |
| Admission RIFLE score | | <.001 |
| None | 357 (53.8) | 39 (32.2) | |
| At risk | 93 (14.0) | 21 (17.4) | |
| Injury | 97 (14.6) | 26 (21.5) | |
| Failure | 116 (17.5) | 35 (28.9) | |
| Evolution of AKI | | <.001 |
| No AKI | 330 (49.8) | 32 (26.4) | |
| Transient AKI | 64 (9.7) | 9 (7.4) | |
| Persistent AKI | 269 (40.6) | 80 (66.1) | |
| Outcome | | | |
| Duration of initial MV, days | 3 [2 - 7] | 4 [2 - 10] | .07 |
| Recurrence of MV | 28 (4.2) | 11 (9.1) | .037 |
| MV-free days<sup>a</sup> | 76 [3 - 87] | 18 [1 - 83] | <.001 |
| Use of RRT<sup>b</sup> | 120 (18.1) | 42 (34.7) | <.001 |
| RRT-free days<sup>c</sup> | 90 [10 - 90] | 46 [2 - 90] | <.001 |
| Complications<sup>c</sup> | | | |
| None | 574 (86.6) | 93 (76.9) | .008 |
| ICU-acquired AKI | 30 (4.5) | 10 (8.3) | .11 |
| ICU-acquired ARDS | 19 (2.9) | 4 (3.3) | .77 |
| ICU-acquired infection | 65 (9.8) | 20 (16.5) | .038 |
| ICU length of stay, days | 5 [3 - 11] | 6 [3 - 14] | .08 |
| Hospital length of stay, days | 17 [7 - 36] | 19 [5 - 35] | .77 |
| ICU-mortality | 172 (25.9) | 55 (45.5) | <.001 |
| 30-day mortality | 214 (32.3) | 53 (43.8) | .016 |
| 60-day mortality | 251 (37.9) | 61 (50.4) | .011 |
| 90-day mortality | 273 (41.2) | 63 (52.1) | .028 |
| 1-year mortality | 340 (51.3) | 70 (57.9) | .20 |
| ICU-free days<sup>d</sup> | 75 [0 - 85] | 25 [0 - 79] | <.001 |

Abbreviations: ABPm, mean arterial blood pressure; ACE, Angiotensin converting enzyme; AKI, acute kidney injury; AMC, Academic medical Center Amsterdam; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; CVP, central venous pressure; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component); UMCU, University Medical Center, Utrecht.

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Wilcoxon rank-sum test. Associations between categorical variables were tested using the Fisher’s exact test.

<sup>a</sup> Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

<sup>b</sup> Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

<sup>c</sup> Other sites of infection: Infections of bones and joints (n=19), Oral infections (n=8), Postoperative wound infections (n=20), Upper respiratory tract infections (n=20), Viral systemic infections (n=6), Endometritis (n=4), Other (n=27).
### Table 16. Baseline characteristics and outcomes of patients admitted to the ICU with septic shock and with plasma biomarkers measured upon admission, stratified according to the presence and evolution of acute kidney injury

|                      | No AKI (n = 209) | Transient AKI (n = 42) | Persistent AKI (n = 233) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**     |                  |                        |                          |         |
| Age, years           | 61 [48 - 70]     | 63 [52 - 72]           | 64 [54 - 72]             | .022    |
| Male sex             | 122 (60.3)       | 22 (52.4)              | 132 (56.7)               | .57     |
| Race, white          | 180 (86.5)       | 36 (85.7)              | 204 (88.7)               | .72     |
| Medical admission    | 148 (70.8)       | 28 (66.7)              | 164 (70.4)               | .85     |
| **Chronic comorbidities** |            |                        |                          |         |
| None                 | 57 (27.3)        | 10 (23.8)              | 64 (27.5)                | .92     |
| Cardiovascular       | 66 (31.6)        | 13 (31.0)              | 63 (27.0)                | .56     |
| Hypertension         | 58 (27.8)        | 20 (47.6)              | 59 (25.3)†               | .016    |
| Diabetes             | 34 (16.3)        | 9 (21.4)               | 41 (17.6)                | .69     |
| Liver cirrhosis      | 5 (2.4)          | 2 (4.8)                | 6 (2.6)                  | .53     |
| Immune compromise    | 49 (23.4)        | 6 (14.3)               | 51 (21.9)                | .44     |
| Malignancy           | 45 (21.5)        | 7 (16.7)               | 61 (26.2)                | .31     |
| Charlson comorbidity index | 3 [1 - 5] | 3 [2 - 5]          | 3 [2 - 5]                | .18     |
| **Chronic medication** |            |                        |                          |         |
| Diuretics            | 41 (19.6)        | 14 (33.3)              | 59 (25.3)                | .11     |
| ACE inhibitors / ARBs| 51 (24.4)        | 10 (23.8)              | 65 (27.9)                | .67     |
| Calcium-entry blockers| 33 (15.8)      | 9 (21.4)               | 32 (13.7)                | .40     |
| Beta-adrenergic blockers | 54 (25.8)   | 13 (31.0)              | 56 (24.0)                | .60     |
| NSAIDs and Cox II inhibitors | 25 (12.0) | 8 (19.0)              | 31 (13.3)                | .44     |
| Oral antidiabetic drugs | 23 (13.9)   | 4 (9.5)                | 22 (9.4)                 | .32     |
| Corticosteroids      | 53 (26.5)        | 8 (19.5)               | 59 (26.1)                | .68     |
| **Severity at time of admission to ICU** |            |                        |                          |         |
| APACHE IV score      | 75 [62 - 95]     | 79 [66 - 93]           | 102 [81 - 120]†‡         | <.001   |
| Acute physiology score | 64 [52 - 80] | 65 [55 - 78]          | 87 [68 - 107]†‡          | <.001   |
| mSOFA score          | 8 [7 - 9]        | 9 [8 - 10]†            | 10 [8 - 13]†‡            | <.001   |
| Non-renal mSOFA score| 7 [6 - 8]        | 8 [7 - 9]              | 8 [7 - 10]†              | <.001   |
| Shock                | 209 (100.0)      | 42 (100.0)             | 233 (100.0)              | >.99    |
| ARDS                 | 83 (39.7)        | 15 (35.7)              | 90 (38.6)                | <.01    |
| **Therapy during the first 24h** |            |                        |                          |         |
| Mechanical ventilation| 204 (97.6)      | 39 (92.9)              | 211 (90.6)               | .004    |
| Vasopressors         | 209 (100.0)      | 42 (100.0)             | 233 (100.0)              | >.99    |
| Dose of vasopressors (mg)a | 10.6 [4.9 - 17.1] | 13.4 [6.0 - 23.4] | 18.8 [9.0 - 39.2]†         | <.001   |
| Inotropes            | 14 (6.7)         | 2 (4.8)                | 49 (21.0)†               | <.001   |
| Dose of inotropes (mg)a | 192.3 [42.1 - 323.7] | 180.7 [161.8 - 199.5] | 221.6 [83.9 - 326.6]     | .84     |
| RRT                  | 3 (1.4)          | 3 (7.1)                | 65 (28.0)†               | <.001   |
| Nephrotic drugs (≥ one) | 108 (51.7)     | 26 (61.9)              | 168 (72.1)†              | <.001   |
| Aminoglycoside       | 40 (19.1)        | 13 (31.0)              | 79 (33.9)                | .002    |
| Glycopeptide         | 33 (15.8)        | 3 (7.1)                | 51 (21.9)                | .040    |
| Colloid              | 68 (32.5)        | 21 (50.0)              | 114 (48.9)               | .001    |
| Otherb               | 14 (6.7)         | 1 (2.4)                | 18 (7.7)                 | .50     |
| **Source of infection** |            |                        |                          |         |
| Pulmonary tract      | 128 (61.2)       | 16 (38.1)†             | 84 (36.1)†               | <.001   |
| Abdominal            | 36 (17.2)        | 16 (38.1)†             | 69 (29.6)†               | .001    |
| Cardiovascular       | 20 (9.6)         | 3 (7.1)                | 28 (12.0)                | .58     |
| Urinary tract        | 7 (3.3)          | 2 (4.8)                | 20 (8.6)                 | .06     |
| CNS                  | 6 (2.9)          | 1 (2.4)                | 4 (1.7)                  | .65     |
| Skin or soft tissue  | 8 (3.8)          | 3 (7.1)                | 17 (7.3)                 | .27     |
| Otherc               | 4 (1.9)          | 1 (2.4)                | 6 (2.6)                  | .90     |
| Unknown              | 0 (0.0)          | 0 (0.0)                | 5 (2.1)                  | .14     |

eTable 16 continued
### Renal function during the first 24 hours

|                      | (n = 209) | Transient AKI (n = 42) | Persistent AKI (n = 233) |
|----------------------|-----------|-----------------------|--------------------------|
| **Creatinine, µmol/L** | 84 [65 - 114] | 138 [96 - 171]* | 174 [132 - 229]*† <.001 |
| **Urea, mmol/L**     | 7.4 [5.3 - 10.2] | 10.8 [9.7 - 18.0]* | 13.3 [9.4 - 18.8]* <.001 |
| **Bicarbonate (minimal), mmol/L** | 20.9 [17.2 - 23.7] | 18.6 [16.6 - 21.4]* | 15.7 [13.6 - 18.6]* <.001 |
| **Urine output, mL** | 1760 [1270 - 2640] | 1398 [931 - 2369] | 880 [395 - 1735]* <.001 |

### Outcome

|                      | (n = 209) | Transient AKI (n = 42) | Persistent AKI (n = 233) |
|----------------------|-----------|-----------------------|--------------------------|
| **Duration of initial MV, days** | 4 [2 - 8] | 5 [2 - 7] | 4 [2 - 9] .89 |
| **Recurrence of MV** | 6 (2.9) | 4 (9.5) | 12 (5.2) .13 |
| **MV-free days\(^d\)** | 82 [13 - 87] | 84 [45 - 88] | 22 [1 - 83]† <.001 |
| **Use of RRT** | 14 (6.7) | 3 (7.1) | 102 (43.8)*† <.001 |
| **RRT-free days\(^d\)** | 90 [35 - 90] | 90 [57 - 90] | 42 [3 - 90]† <.001 |

### Complications\(^e\)

|                      | (n = 209) | Transient AKI (n = 42) | Persistent AKI (n = 233) |
|----------------------|-----------|-----------------------|--------------------------|
| **None** | 174 (83.3) | 35 (83.3) | 192 (82.4) .98 |
| **ICU-acquired AKI** | 22 (10.5) | 2 (4.8) | 9 (3.9)* .018 |
| **ICU-acquired ARDS** | 9 (4.3) | 1 (2.4) | 8 (3.4) .93 |
| **ICU-acquired infection** | 20 (9.6) | 6 (14.3) | 33 (14.2) .29 |
| **ICU length of stay, days** | 6 [4 - 11] | 7 [4 - 12] | 7 [3 - 13] .66 |
| **Hospital length of stay, days** | 20 [11 - 43] | 23 [14 - 42] | 17 [5 - 38] .016 |
| **ICU-mortality** | 37 (17.7) | 5 (11.9) | 101 (43.3)*† <.001 |
| **30-day mortality** | 51 (24.4) | 8 (19.0) | 104 (44.6)*† <.001 |
| **60-day mortality** | 64 (30.6) | 11 (26.2) | 121 (51.9)*† <.001 |
| **90-day mortality** | 72 (34.4) | 11 (26.2) | 129 (55.4)*† <.001 |
| **1-year mortality** | 96 (45.9) | 16 (38.1) | 149 (63.9)*† <.001 |
| **ICU-free days\(^d\)** | 79 [15 - 85] | 81 [50 - 85] | 29 [0 - 81]† <.001 |

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**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson $\chi^2$ test or the Fisher’s exact test when appropriate. $P$ value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

\(^a\) Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

\(^b\) Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

\(^c\) Other sites of infection: Infections of bones and joints (n=4), Postoperative wound infections (n=3), Upper respiratory tract infections (n=3), Viral systemic infections (n=1)

\(^d\) Between inclusion and day-90.

\(^e\) Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
eTable 17. Host response biomarkers in patients with septic shock during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission

|                    | No AKI (n= 209) | Transient AKI (n= 42) | Persistent AKI (n= 233) | No AKI (n= 181) | Transient AKI (n= 42) | Persistent AKI (n= 179) | No AKI (n= 122) | Transient AKI (n= 27) | Persistent AKI (n= 134) | P Value (group) | P Value (time x group) |
|--------------------|-----------------|-----------------------|-------------------------|-----------------|-----------------------|-------------------------|-----------------|----------------------|-------------------------|----------------|-----------------------|
| **Inflammatory responses** |                 |                       |                         |                 |                       |                         |                 |                       |                         |                |                       |
| IL-10 (pg/mL)                  | 10.8 (4.1-33.0) | 29.2 (9.1-91.8)       | 54.0 (14.9-244.4)      | 5.4 (2.3-10.9)  | 7.0 (3.7-12.3)        | 18.1 (7.6-78.8)†       | 4.2 (2.2-10.5)   | 4.5 (2.9-6.6)        | 14.1 (4.8-35.0)†      | <.001          | .002                  |
| Fractalkine (ng/mL)             | 165.7 (39.9-1364.8) | 487.1 (201.4-2562.8)  | 828.5 (191.1-1616)     | 52.1 (19.1-161.6) | 91.1 (35.5-197.8)†    | 141.1 (36.2-1081.2)†   | 44.6 (12.3-138.2) | 26.3 (10.3-68.4)     | 53.9 (19.3-125.9)†     | <.001          | <.001                 |
| IL-8 (pg/mL)                   | 91.1 (34.1-302.7) | 223.7 (126.4-687.1)   | 567.4 (127.9-2720.4)†  | 47.8 (22.5-122.9) | 113.4 (41.7-189.3)†   | 201.3 (76.2-808.6)†     | 36.6 (16.6-127.7) | 59.2 (36.1-80.3)     | 110.5 (61.3-274.6)†    | <.001          | .003                  |
| MMP-8 (ng/mL)                  | 2.8 (0.9-7.9)    | 9.4 (1.9-19.1)        | 6.7 (0.6-5.2)          | 1.9 (0.6-5.2)  | 4.1 (1.3-10.9)        | 5.3 (1.2-16.1)†         | 1.2 (0.4-2.6)   | 1.3 (0.7-5.3)        | 3.2 (0.8-8.4)†         | <.001          | .27                   |
| **Endothelial cell activation** |                 |                       |                         |                 |                       |                         |                 |                       |                         |                |                       |
| Fractalkine (pg/mL)            | 22.6 (13.4-48.9) | 34.3 (15.2-58.2)      | 54.2 (12.8-38.4)†‡     | 19.1 (12.8-38.4) | 28.4 (13.4-49.2)†      | 55.8 (23.1-123.9)†      | 20.4 (13.4-46.9) | 33.1 (16.7-54.0)     | 63.5 (32.8-140.6)†     | <.001          | .012                  |
| sE-Selectin (ng/mL)            | 9.9 (3.9-22.7)   | 12.1 (5.6-32.5)       | 14.0 (5.7-31.0)†       | 10.1 (4.0-19.2) | 11.4 (4.7-22.2)       | 11.2 (4.9-23.1)†        | 7.7 (4.3-18.0)  | 7.3 (4.4-13.9)       | 8.4 (4.5-17.4)†        | .19            | .010                  |
| sICAM-1 (ng/mL)                | 163.2 (87.2-309.7) | 205.5 (105.4-391.5)   | 231.3 (123.9-366.1)*   | 196.2 (112.0-320.8) | 256.2 (115.7-431.9)   | 269.2 (143.8-426.2)*†    | 239.5 (129.3-342.2) | 194.0 (122.0-363.0)  | 264.2 (176.0-414.3)*†  | <.001          | .30                   |
| Angiopoietin-1 (ng/mL)         | 2.4 (1.0-6.6)    | 4.1 (1.2-9.9)         | 1.5 (0.7-3.4)†         | 2.0 (0.8-4.8)  | 1.7 (0.8-3.5)         | 1.0 (0.6-2.0)†          | 2.0 (0.9-4.8)  | 1.6 (1.0-3.6)        | 0.7 (0.4-1.9)†         | <.001          | .13                   |
| Angiopoietin-2 (ng/mL)         | 6.0 (2.6-11.7)   | 9.6 (4.2-23.9)        | 13.2 (5.7-28.2)†       | 7.1 (3.6-14.5) | 12.3 (5.1-21.5)       | 18.6 (10.3-47.3)†        | 2.7 (2.1-11.2) | 3.7 (3.8-7.0)        | 9.5 (4.3-23.7)†        | <.001          | .36                   |
| ANG-2:ANG-1 (pg/mL)            | 2.1 (0.6-9.0)    | 2.4 (0.8-14.5)        | 8.4 (2.4-30.0)†        | 3.7 (1.2-12.3) | 7.8 (1.8-20.9)        | 24.1 (7.9-59.4)†         | 0.7 (0.7-9.6)  | 1.8 (1.8-6.8)        | 4.5 (4.5-38.6)†        | <.001          | .98                   |
### eTable 17 continued

|                         | No AKI (n = 162) | Transient AKI (n = 54) | Persistent AKI (n = 116) | Day-2 | No AKI (n = 137) | Transient AKI (n = 54) | Persistent AKI (n = 86) | Day 4 | No AKI (n = 87) | Transient AKI (n = 37) | Persistent AKI (n = 66) | P Value (group) | P Value (time x group) |
|------------------------|------------------|------------------------|--------------------------|-------|------------------|------------------------|--------------------------|-------|----------------|------------------------|--------------------------|-----------------|---------------------|
| **Coagulation activation** |                  |                        |                          |       |                  |                        |                          |       |                |                        |                          |                 |                     |
| D-dimer (µg/mL)        | 8.0 [4.0 - 14.7] | 9.3 [4.2 - 18.0]       | 12.0 [6.2 - 22.3]*       | 6.7   | 11.8 [3.6 - 14.5] | 14.5 [6.0 - 23.1]*     | 8.4 [4.3 - 18.6]         | 8.5   | 13.0           | 128.9 [78.7 - 169.2] | 160.0 [79.7 - 231.1] | <.001           | .81                 |
| Protein C (ng/mL)      | 112.5 [86.1 - 146.1] | 110.1 [74.5 - 121.8]* | 117.9 [91.4 - 156.0]     | 128.9 | 121.6 [101.7 - 169.2] | 112.8 [85.4 - 140.7]* | 110.7 [79.7 - 157.5]     | 111.0 | 110.0         | 936.8 [668.0 - 1414.0] | 696.9 [430.2 - 1031.3†] | .001            | .47                 |
| Antithrombin (ng/mL)   | 688.0 [455.3 - 958.2] | 633.7 [396.8 - 980.1] | 597.2 [388.5 - 929.9]    | 671.7 | 645.8 [393.0 - 960.4] | 545.5 [381.9 - 823.8] | 899.7 [534.2 - 1414.0]     | 936.8 | 696.9         | 936.8 [668.0 - 1414.0] | 696.9 [430.2 - 1031.3†] | .11              | .049                |
| PT (sec)               | 15.3 [12.9 - 14.8] | 14.8 [12.6 - 16.0]    | 17.5 [14.4 - 23.0]*†    | 15.0  | 13.0 [12.0 - 17.0] | 16.0 [11.8 - 20.0]*†   | 14.0 [12.0 - 16.0]        | 12.0  | 15.0          | 12.0 [11.0 - 16.0] | 12.0 [11.0 - 16.0] | <.001           | .008                |
| aPTT (sec)             | 37.0 [29.5 - 42.0] | 35.5 [30.5 - 41.2] | 47.0 [37.0 - 64.8]*†       | 39.0   | 35.5 [29.0 - 30.2] | 46.0 [30.2 - 58.8]*†     | 32.5 [27.2 - 50.5]         | 27.0  | 40.0           | 27.0 [25.5 - 31.0] | 33.0 [25.0 - 48.0†] | <.001           | .17                 |
| Platelets (10^9/L)     | 177.5 [117.0 - 249.5] | 185.0 [119.0 - 236.2] | 116.0 [50.0 - 209.0]*†   | 174.0 | 147.0 [102.2 - 247.2] | 115.0 [76.0 - 203.0] | 172.0 [108.0 - 263.0]    | 168.0 | 88.5          | 88.0 [80.2 - 218.8] | 172.5 [120.0 - 218.8] | <.001           | .032                |

**Abbreviations:** ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Data presented as median [interquartile range]

Overall P values are derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn’s post hoc tests of multiple comparisons using rank sums.

* Significant vs no AKI
† Significant vs Transient AKI
### Table 18. Baseline characteristics and outcomes of patients admitted to the ICU with septic shock and with blood genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury

| Demographics | No AKI (n = 91) | Transient AKI (n = 25) | Persistent AKI (n = 109) | P Value |
|--------------|-----------------|------------------------|--------------------------|---------|
| Age, years   | 63 [52 - 70]    | 62 [49 - 74]           | 64 [56 - 72]             | .44     |
| Male sex     | 51 (56.0)       | 12 (48.0)              | 62 (56.9)                | .74     |
| Race, white  | 76 (84.4)       | 21 (84.0)              | 92 (86.8)                | .83     |
| Medical admission | 60 (65.9) | 17 (68.0)              | 71 (65.1)                | >.99    |
| Chronic comorbidities | | | | |
| None         | 24 (26.4)       | 6 (24.0)               | 40 (36.7)                | .23     |
| Cardiovascular compromise | 27 (29.7) | 7 (28.0)               | 22 (20.2)                | .27     |
| Hypertension | 28 (30.8)       | 12 (48.0)              | 26 (23.9)                | .06     |
| Diabetes     | 17 (18.7)       | 5 (20.0)               | 22 (20.2)                | .97     |
| Liver cirrhosis | 2 (2.2)   | 0 (0.0)                | 2 (1.8)                  | >.99    |
| Malignancy   | 25 (27.5)       | 5 (20.0)               | 18 (16.5)                | .16     |
| Charlson comorbidity index | 4 [2 - 5] | 3 [2 - 5]              | 3 [2 - 4]                | .83     |
| Chronic medication | | | | |
| Diuretics    | 17 (18.7)       | 10 (40.0)              | 32 (28.4)                | .06     |
| ACE inhibitors / ARBs | 21 (23.1) | 6 (24.0)               | 31 (28.4)                | .69     |
| Calcium-entry blockers | 17 (18.7) | 6 (24.0)               | 14 (12.8)                | .29     |
| Beta-adrenergic blockers | 23 (25.3) | 7 (28.0)               | 37 (33.9)                | .40     |
| NSAIDs and Cox II inhibitors | 13 (14.3) | 6 (24.0)               | 10 (9.2)                 | .12     |
| Oral antidiabetic drugs | 8 (8.8) | 4 (16.0)               | 20 (18.3)                | .14     |
| Corticosteroids | 15 (16.5) | 2 (8.0)                | 6 (5.5)                  | .029    |
| Antiplatelet drugs | 28 (32.9) | 5 (20.8)               | 30 (28.0)                | .51     |
| Severity at time of admission to ICU | | | | |
| APACHE IV score | 79 [65 - 96] | 87 [75 - 96]           | 95 [78 - 116]*           | <.001   |
| Acute physiology score | 66 [53 - 80] | 70 [64 - 80]           | 84 [65 - 106]*           | <.001   |
| mSOFA score   | 8 [7 - 9]      | 9 [8 - 10]             | 10 [9 - 13]*             | <.001   |
| Non-renal mSOFA score | 7 [6 - 8] | 8 [7 - 9]               | 8 [7 - 10]*              | <.001   |
| Shock         | 91 (100.0)     | 25 (100.0)             | 109 (100.0)              | >.99    |
| ARDS          | 36 (39.6)      | 9 (36.0)               | 46 (42.2)                | .84     |
| Therapy during the first 24h | | | | |
| Mechanical ventilation | 89 (97.8) | 24 (96.0)              | 103 (94.5)               | .48     |
| Vasopressors  | 91 (100.0)     | 25 (100.0)             | 109 (100.0)              | >.99    |
| Dose of vasopressors (mg)* | 10.0 [5.1 - 17.6] | 17.5 [6.3 - 34.5]* | 19.2 [10.4 - 39.4]* | <.001 |
| Dose of vasopressors (mg)* | 7 (7.7) | 2 (8.0)                | 27 (24.8)*               | .002    |
| RRT           | 0 (0.0)        | 0 (0.0)                | 35 (32.1)*               | <.001   |
| Source of infection | | | | |
| Pulmonary tract | 53 (58.2) | 11 (44.0)              | 39 (35.8)*               | .007    |
| Abdominal     | 17 (18.7)      | 10 (40.0)              | 36 (33.0)                | .025    |
| Cardiovascular | 9 (9.9)        | 0 (0.0)                | 13 (11.9)                | .22     |
| Urinary tract | 4 (4.4)        | 1 (4.0)                | 11 (10.1)                | .27     |
| CNS           | 2 (2.2)        | 0 (0.0)                | 1 (0.9)                  | .71     |
| Skin or soft tissue | 5 (5.5) | 2 (8.0)                | 8 (7.3)                  | .80     |
| Other c       | 1 (1.1)        | 1 (4.0)                | 0 (0.0)                  | .10     |
| Unknown       | 0 (0.0)        | 0 (0.0)                | 1 (0.9)                  | >.99    |
### Renal function during the first 24 hours

|                          | No AKI (n = 91) | Transient AKI (n = 25) | Persistent AKI (n = 109) | P Value |
|--------------------------|-----------------|------------------------|--------------------------|---------|
| **Creatinine, µmol/L**   | 84 [66 - 115]   | 144 [110 - 171]*      | 174 [140 - 239]*         | <.001   |
| **Urea, mmol/L**         | 7.4 [5.4 - 9.9] | 14.6 [10.2 - 19.5]*    | 13.0 [9.3 - 17.8]*       | <.001   |
| **Bicarbonate (minimal), mmol/L** | 19.5 [16.7 - 23.6] | 18.2 [15.9 - 20.4] | 15.7 [13.1 - 18.5]†     | <.001   |
| **Urine output, mL**     | 1655 [1200 - 2583] | 1595 [1180 - 2380] | 940 [365 - 1335]*       | <.001   |

### Outcome

|                          |                  |                      |                          |         |
|--------------------------|------------------|----------------------|--------------------------|---------|
| **Duration of initial MV, days** | 4 [2 - 10]     | 6 [3 - 10]           | 5 [2 - 10]               | .84     |
| **Recurrent of MV**      | 3 (3.3)         | 3 (12.0)             | 8 (7.3)                  | .17     |
| **MV-free days**         | 79 [30 - 87]    | 79 [27 - 87]         | 42 [1 - 82]†            | <.001   |
| **Use of RRT**           | 7 (7.7)         | 1 (4.0)              | 54 (49.5)†              | <.001   |
| **RRT-free days**        | 90 [50 - 90]    | 90 [46 - 90]         | 60 [2 - 90]†            | <.001   |

### Complications

|                          |                  |                      |                          |         |
|--------------------------|------------------|----------------------|--------------------------|---------|
| **None**                 | 77 (84.6)        | 19 (76.0)            | 87 (79.8)                | .52     |
| **ICU-acquired AKI**     | 11 (12.1)        | 2 (8.0)              | 7 (6.4)                  | .39     |
| **ICU-acquired ARDS**    | 2 (2.2)          | 1 (4.0)              | 3 (2.8)                  | .71     |
| **ICU-acquired infection** | 5 (5.5)         | 4 (16.0)             | 17 (15.6)                | .049    |
| **ICU length of stay, days** | 6 [4 - 12]     | 8 [6 - 12]           | 9 [4 - 14]               | .34     |
| **Hospital length of stay, days** | 18 [11 - 49]   | 26 [15 - 50]         | 21 [6 - 45]              | .22     |
| **ICU-mortality**        | 16 (17.6)        | 3 (12.0)             | 45 (41.3)†               | <.001   |
| **30-day mortality**     | 20 (22.0)        | 5 (20.0)             | 50 (45.9)*               | .001    |
| **60-day mortality**     | 26 (28.6)        | 7 (28.0)             | 52 (47.7)*               | .012    |
| **90-day mortality**     | 29 (31.9)        | 7 (28.0)             | 56 (51.4)*               | .008    |
| **1-year mortality**     | 40 (44.0)        | 10 (40.0)            | 65 (59.6)                | .044    |
| **ICU-free days**        | 78 [34 - 84]     | 78 [25 - 83]         | 47 [0 - 79]†             | <.001   |

**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ2 test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

* Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

b Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

c Other sites of infection: Infections of bones and joints (n=1), Postoperative wound infections (n=1).

d Between inclusion and day-90.

e Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### eTable 19. Baseline characteristics and outcomes of patients admitted to the ICU with septic shock of short duration (< 52 hours) and with plasma biomarkers measured upon admission, stratified according to the presence and evolution of acute kidney injury

|                                | No AKI (n = 126) | Transient AKI (n = 26) | Persistent AKI (n = 110) | P Value |
|--------------------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**               |                  |                        |                          |         |
| Age, years                     | 61 [49 - 71]     | 67 [52 - 73]           | 64 [57 - 72]             | .19     |
| Male sex                       | 76 (60.3)        | 13 (50.0)              | 67 (60.9)                | .58     |
| Race, white                    | 111 (88.1)       | 21 (80.8)              | 91 (84.3)                | .48     |
| Medical admission              | 85 (67.5)        | 18 (69.2)              | 78 (70.9)                | .85     |
| **Chronic comorbidities**      |                  |                        |                          |         |
| None                           | 35 (27.8)        | 4 (15.4)               | 32 (29.1)                | .39     |
| Cardiovascular compromise      | 38 (30.2)        | 10 (38.5)              | 27 (24.5)                | .33     |
| Hypertension                   | 37 (29.4)        | 13 (50.0)              | 25 (22.7)†              | .024    |
| Diabetes                       | 22 (17.5)        | 8 (30.8)               | 21 (19.1)                | .31     |
| Liver cirrhosis                | 3 (2.4)          | 2 (7.7)                | 4 (3.6)                  | .30     |
| Immune compromise              | 31 (24.6)        | 5 (19.2)               | 22 (20.0)                | .68     |
| Malignancy                     | 19 (15.1)        | 4 (15.4)               | 33 (30.0)*               | .016    |
| Charlson comorbidity index     | 3 [1 - 4]        | 4 [2 - 5]              | 3 [2 - 5]                | .23     |
| **Chronic medication**         |                  |                        |                          |         |
| Diuretics                      | 26 (20.6)        | 9 (34.6)               | 26 (23.6)                | .30     |
| ACE inhibitors / ARBs          | 37 (29.4)        | 6 (23.1)               | 27 (24.5)                | .68     |
| Calcium-entry blockers         | 21 (16.7)        | 6 (23.1)               | 13 (11.8)                | .28     |
| Beta-adrenergic blockers       | 38 (30.2)        | 7 (26.9)               | 32 (29.1)                | .96     |
| NSAIDs and Cox II inhibitors   | 15 (11.9)        | 5 (19.2)               | 19 (17.3)                | .36     |
| Oral antidiabetic drugs        | 12 (9.5)         | 7 (26.9)               | 14 (12.7)                | .06     |
| Corticosteroids                | 20 (15.9)        | 4 (15.4)               | 12 (10.9)                | .49     |
| Antiplatelet drugs             | 32 (26.4)        | 6 (23.1)               | 30 (28.0)                | .92     |
| **Severity at time of admission to ICU** |              |                        |                          |         |
| APACHE IV score                | 75 [60 - 95]     | 79 [66 - 93]           | 104 [78 - 127]**†       | <.001   |
| Acute physiology score         | 63 [49 - 78]     | 65 [50 - 77]           | 88 [68 - 115]**†        | <.001   |
| mSOFA score                    | 7 [6 - 9]        | 8 [7 - 9]              | 11 [8 - 13]**†          | <.001   |
| Non-renal mSOFA score          | 7 [6 - 8]        | 7 [6 - 8]              | 8 [7 - 10]**†           | <.001   |
| Shock                          | 126 (100.0)      | 26 (100.0)             | 110 (100.0)              | >.99    |
| ARDS                           | 50 (39.7)        | 10 (38.5)              | 37 (33.6)                | .63     |
| **Therapy during the first 24h** |                  |                        |                          |         |
| Mechanical ventilation         | 124 (98.4)       | 23 (88.5)              | 99 (90.0)*               | .007    |
| Vasopressors                   | 126 (100.0)      | 26 (100.0)             | 110 (100.0)              | >.99    |
| Dose of vasopressors (mg)*     | 7.8 [3.5 - 13.0] | 7.6 [3.5 - 12.7]       | 13.3 [5.6 - 37.3]**†    | <.001   |
| Inotropes                      | 5 (4.0)          | 0 (0.0)                | 16 (14.5)*               | .004    |
| Dose of inotropes (mg)*        | 150.2 [86.6 - 344.8] | NA                     | 115.4 [46.7 - 252.9]   | .41     |
| RRT                            | 2 (1.6)          | 3 (11.5)               | 25 (22.9)*               | <.001   |
| Nephrotoxic drugs (≥ one)      | 63 (50.0)        | 15 (57.7)              | 77 (70.0)*               | .007    |
| Aminoglycoside                 | 21 (16.7)        | 5 (19.2)               | 35 (31.8)*               | .023    |
| Glycopeptide                   | 18 (14.3)        | 2 (7.7)                | 28 (25.5)                | .035    |
| Colloid                        | 40 (31.7)        | 13 (50.0)              | 46 (41.8)                | .11     |
| Other                          | 6 (4.8)          | 1 (3.8)                | 9 (8.2)                  | .56     |
| **Source of infection**        |                  |                        |                          |         |
| Pulmonary tract                | 79 (62.7)        | 11 (42.3)              | 34 (30.9)*               | <.001   |
| Abdominal                      | 19 (15.1)        | 8 (30.8)               | 39 (35.5)*               | .001    |
| Cardiovascular                 | 12 (9.5)         | 3 (11.5)               | 11 (10.0)                | .91     |
| Urinary tract                  | 4 (3.2)          | 1 (3.8)                | 12 (10.9)                | .048    |
| CNS                            | 6 (4.8)          | 1 (3.8)                | 0 (0.0)                  | .05     |
| Skin or soft tissue            | 4 (3.2)          | 2 (7.7)                | 8 (7.3)                  | .28     |
| Other                          | 2 (1.6)          | 0 (0.0)                | 3 (2.7)                  | .80     |
| Unknown                        | 0 (0.0)          | 0 (0.0)                | 3 (2.7)                  | .22     |
## eTable 19 continued

| Renal function during the first 24 hours | No AKI (n = 126) | Transient AKI (n = 26) | Persistent AKI (n = 110) | P Value |
|----------------------------------------|-----------------|------------------------|------------------------|--------|
| Creatinine, µmol/L                     | 84 [60 - 114]   | 130 [85 - 197]*        | 171 [144 - 235]†       | <.001  |
| Urea, mmol/L                           | 7.4 [5.4 - 10.2]| 10.6 [10.3 - 19.3]*    | 13.9 [10.7 - 19.1]*    | <.001  |
| Bicarbonate (minimal), mmol/L          | 21.6 [18.3 - 25.0] | 18.6 [15.4 - 20.7]*    | 15.4 [12.6 - 18.8]†    | <.001  |
| Urine output, mL                       | 1938 [1370 - 2996] | 1308 [885 - 2286]     | 848 [316 - 1351]†      | <.001  |

### Outcome

| Duration of initial MV, days | 2 [2 - 5] | 3 [2 - 5.75] | 2 [1 - 4] | .06 |
|-----------------------------|-----------|--------------|-----------|-----|
| Recurrence of MV            | 3 (2.4)   | 2 (7.7)      | 4 (3.6)   | .30 |
| MV-free daysd               | 85 [26 - 88] | 85 [23 - 88] | 21 [1 - 87]† | <.001 |
| Use of RRT                  | 3 (2.4)   | 3 (11.5)     | 35 (31.8)* | <.001 |
| RRT-free daysd              | 90 [52 - 90] | 90 [30 - 90] | 47 [2 - 90]† | <.001 |

### Complications

| None                        | 116 (92.1) | 23 (88.5) | 98 (89.1) | .65 |
|------------------------------|------------|-----------|-----------|-----|
| ICU-acquired AKI             | 6 (4.8)    | 1 (3.8)   | 1 (0.9)   | .15 |
| ICU-acquired ARDS            | 3 (2.4)    | 0 (0.0)   | 4 (3.6)   | .86 |
| ICU-acquired infection       | 5 (4.0)    | 2 (7.7)   | 10 (9.1)  | .22 |
| ICU length of stay, days     | 4 [3 - 8]  | 6 [4 - 8]  | 3 [2 - 8]† | .038 |
| Hospital length of stay, days| 17 [10 - 35]| 19 [12 - 40]| 15 [3 - 31]†| .017 |
| ICU-mortality                | 13 [10.3]  | 4 [15.4]   | 47 [42.7]* | <.001 |
| 30-day mortality             | 28 [22.2]  | 7 [26.9]   | 50 [45.5]* | .001 |
| 60-day mortality             | 35 [27.8]  | 8 [30.8]   | 57 [51.8]* | .002 |
| 90-day mortality             | 40 [31.7]  | 8 [30.8]   | 59 [53.6]* | .036 |
| 1-year mortality             | 59 [46.8]  | 12 [46.2]  | 69 [62.7]* | .001 |
| ICU-free daysd               | 82 [36 - 86] | 84 [23 - 86] | 34 [0 - 85]* | .001 |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher's exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

a Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

b Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

c Other sites of infection: Infections of bones and joints (n=1), Postoperative wound infections (n=3), Upper respiratory tract infections (n=1).

d Between inclusion and day-90.

* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
## eTable 20. Host response biomarkers in patients with septic shock of short duration (< 52 hours) during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission

| Inflammatory responses | Admission | Day-2 | Day 4 |
|------------------------|-----------|-------|-------|
| **IL-10** (pg/mL) | 8.7 [4.1 - 27.6] | 4.6 [2.1 - 9.2] | 2.9 [2.0 - 5.4] |
| **IL-6** (pg/mL) | 124.0 [36.6 - 851.6] | 34.7 [16.6 - 133.4] | 42.1 [11.4 - 87.7] |
| **IL-8** (pg/mL) | 87.7 [29.2 - 243.1] | 38.6 [20.3 - 80.9] | 31.4 [17.2 - 131.3] |
| **MMP-8** (ng/mL) | 3.6 [0.6 - 9.2] | 1.8 [0.6 - 4.8] | 1.0 [0.4 - 2.3] |

| Endothelial cell activation | Admission | Day-2 | Day 4 |
|-----------------------------|-----------|-------|-------|
| **Fractalkine** (pg/mL) | 19.9 [13.2 - 37.2] | 15.6 [11.2 - 31.3] | 14.2 [11.0 - 27.7] |
| **sE-Selectin** (ng/mL) | 9.5 [3.9 - 21.4] | 9.9 [4.1 - 15.1] | 7.6 [4.1 - 15.1] |
| **sICAM-1** (ng/mL) | 151.8 [83.7 - 318.4] | 180.6 [117.7 - 277.4] | 185.0 [112.7 - 312.8] |
| **Angiopoietin-1** (pg/mL) | 2.7 [1.0 - 6.7] | 0.9 [0.8 - 1.2] | 1.3 [1.3 - 6.9] |
| **Angiopoietin-2** (ng/mL) | 5.9 [2.5 - 11.0] | 6.1 [4.1 - 10.7] | 4.2 [2.2 - 8.6] |
| **ANG-2:ANG-1** | 2.1 [0.5 - 7.5] | 2.3 [0.7 - 10.5] | 1.4 [0.4 - 4.9] |

| P Value (group) | P Value (time x group) |
|-----------------|------------------------|
| <.001           | .08                    |
| <.001           | .04                    |
| <.001           | .015                   |
| <.001           | .40                    |
| <.001           | .25                    |
| <.001           | .73                    |
| .015            | .12                    |
| .017            | .21                    |
| <.001           | .83                    |
### eTable 20 continued

|                  | No AKI (n=...) | Transient AKI (n=...) | Persistent AKI (n=...) | No AKI (n=...) | Transient AKI (n=...) | Persistent AKI (n=...) | No AKI (n=...) | Transient AKI (n=...) | Persistent AKI (n=...) | P Value (group) | P Value (time x group) |
|------------------|----------------|----------------------|-----------------------|----------------|----------------------|-----------------------|----------------|----------------------|-----------------------|-----------------|-------------------------|
| **Coagulation activation** |                |                      |                       |                |                      |                       |                |                      |                       |                 |                         |
| D-dimer (µg/mL) | 9.1 [3.0 - 15.2] | 8.8 [4.2 - 18.0]     | 13.6 [7.1 - 22.4]†   | 6.1 [3.3 - 12.9] | 10.1 [5.4 - 15.1] † | 16.8 [9.9 - 24.1] †   | 8.5 [3.7 - 17.9] | 5.7 [3.7 - 8.4] † | 13.7 [8.2 - 22.8] † | <.001 | .84                     |
| Protein C (ng/mL) | 112.5 [84.5 - 147.1] | 86.2 [73.1 - 138.8] | 110.8 [85.2 - 141.1] | 122.1 [93.4 - 164.9] | 92.9 [74.5 - 115.9] | 119.5 [93.4 - 148.5] | 125.0 [98.7 - 162.5] | 121.6 [83.8 - 142.5] | 122.6 [77.8 - 205.7] | 0.047 | 0.84                   |
| Antithrombin (ng/mL) | 712.1 [513.2 - 957.8] | 633.7 [472.4 - 963.9] | 644.3 [387.0 - 1012.2] | 702.5 [417.7 - 1008.7] | 650.9 [391.9 - 1022.2] | 671.6 [422.4 - 1433.2] | 962.8 [606.6 - 1499.7] | 936.8 [695.3 - 1593.7] | 869.2 [509.9 - 1593.7] | .51 | .77                     |
| PT (sec) | 14.8 [12.3 - 17.6] | 13.9 [12.6 - 17.2] | 17.1 [14.3 - 22.8]† | 14.0 [12.0 - 16.0] | 13.0 [11.2 - 14.8] | 15.0 [13.0 - 20.0]† | 13.0 [11.5 - 15.0] | 12.0 [11.0 - 14.8] | 14.0 [12.0 - 16.0] | <.001 | .40                     |
| aPTT (sec) | 35.0 [29.0 - 51.5] | 34.0 [28.5 - 39.0] | 47.0 [36.0 - 64.0]† | 35.0 [28.2 - 47.8] | 34.0 [30.0 - 36.0] | 39.5 [30.8 - 58.2] | 32.0 [26.5 - 45.5] | 30.0 [27.0 - 32.5] | 35.0 [28.0 - 44.0] | .002 | .25                     |
| Platelets (10^9/L) | 192.0 [136.0 - 261.0] | 201.0 [135.2 - 263.5] | 116.0 [44.5 - 218.8]† | 192.0 [130.0 - 262.0] | 171.0 [93.0 - 231.0] | 107.0 [43.0 - 199.0] | 221.5 [142.2 - 321.8] | 183.0 [130.5 - 287.0] | 89.0 [25.0 - 202.0]† | <.001 | .19                     |

**Abbreviations:** ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Data presented as median [interquartile range]

Overall P values are derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn's post hoc tests of multiple comparisons using rank sums.

* Significant vs no AKI
† Significant vs Transient AKI
| Demographics | No AKI (n = 54) | Transient AKI (n = 12) | Persistent AKI (n = 46) | P Value |
|--------------|----------------|------------------------|-------------------------|---------|
| Age, years   | 62 [48 - 70]  | 65 [49 - 74]           | 65 [58 - 73]           | .22     |
| Male sex     | 30 (55.6)     | 5 (41.7)               | 32 (69.6)              | .15     |
| Race, white  | 46 (85.2)     | 10 (83.3)              | 38 (86.4)              | >.99    |
| Medical admission | 33 (61.1) | 8 (66.7)              | 29 (63.0)              | >.99    |
| Chronic comorbidities |     |                       |                        |         |
| None         | 15 (27.8)     | 2 (16.7)               | 18 (39.1)              | .29     |
| Cardiovascular compromise | 15 (27.8) | 4 (33.3)               | 7 (15.2)               | .19     |
| Hypertension | 16 (29.6)     | 6 (50.0)               | 12 (26.1)              | .29     |
| Diabetes     | 8 (14.8)      | 4 (33.3)               | 11 (23.9)              | .27     |
| Liver cirrhosis | 1 (1.9)     | 0 (0.0)                | 2 (4.3)                | .71     |
| Immune compromise | 15 (27.8) | 3 (25.0)               | 8 (17.4)               | .45     |
| Malignancy   | 9 (16.7)      | 2 (16.7)               | 9 (19.6)               | .94     |
| Charlson comorbidity index | 3 (1 - 4) | 3 [2 - 5]             | 3 [2 - 5]             | .53     |
| Chronic medication |     |                       |                        |         |
| Diuretics    | 8 (14.8)      | 5 (41.7)               | 13 (28.3)              | .07     |
| ACE inhibitors / ARBs | 11 (20.4) | 3 (25.0)               | 18 (39.1)              | .11     |
| Calcium-entry blockers | 7 (13.0) | 4 (33.3)               | 5 (10.9)               | .16     |
| Beta-adrenergic blockers | 12 (22.2) | 3 (25.0)               | 20 (43.5)              | .06     |
| NSAIDs and Cox II inhibitors | 7 (13.0) | 4 (33.3)               | 5 (10.9)               | .16     |
| Oral antidiabetic drugs | 1 (1.9) | 4 (33.3)*              | 10 (21.7)*             | .001    |
| Corticosteroids | 11 (20.4) | 2 (16.7)               | 9 (19.6)               | .043    |
| Antiplatelet drugs | 16 (31.4) | 3 (25.0)               | 16 (35.6)              | .84     |
| Severity at time of admission to ICU |     |                       |                        |         |
| APACHE IV score | 60 [64 - 98] | 88 [80 - 99]           | 96 [77 - 123]*         | .012    |
| Acute physiology score | 67 [53 - 80] | 72 [65 - 83]           | 82 [66 - 107]*         | .006    |
| mSOFA score | 8 [6 - 8]     | 9 [7 - 9]              | 11 [9 - 13]*           | <.001   |
| Non-renal mSOFA score | 7 [6 - 8] | 7 [7 - 9]              | 9 [7 - 10]*            | <.001   |
| Shock        | 54 (100.0)    | 12 (100.0)             | 46 (100.0)             | >.99    |
| ARDS         | 21 (38.9)     | 4 (33.3)               | 16 (34.8)              | .92     |
| Therapy during the first 24h |     |                       |                        |         |
| Mechanical ventilation | 52 (96.3) | 11 (91.7)             | 45 (97.8)              | .45     |
| Vasopressors | 54 (100.0)    | 12 (100.0)             | 46 (100.0)             | >.99    |
| Dose of vasopressors (mg)a | 7.1 [4.1 - 12.7] | 5.1 [2.8 - 13.4] | 18.1 [6.5 - 45.6]†‡ | .002     |
| Inotropes    | 4 [7.4]       | 0 (0.0)                | 12 (26.1)*             | .010    |
| Dose of inotropes (mg)a | 247.5 [134.3 - 350.0] | NA | 75.5 [54.1 - 150.4] | .07     |
| RRT          | 0 (0.0)       | 0 (0.0)                | 11 (23.9)*             | <.001   |
| Nephrotoxic drugs (≥ one) | 30 (55.6) | 8 (66.7)               | 39 (84.8)*             | .005    |
| Aminoglycoside | 10 (18.5) | 2 (16.7)               | 14 (30.4)              | .34     |
| Glycopeptide | 10 (18.5)     | 1 (8.3)                | 5 (10.9)               | .58     |
| Colloid      | 22 (40.7)     | 8 (66.7)               | 29 (63.0)              | .05     |
| Other b      | 0 (0.0)       | 1 (8.3)                | 2 (4.3)                | .08     |
| Source of infection |     |                       |                        |         |
| Pulmonary tract | 29 (53.7) | 6 (50.0)               | 16 (34.8)              | .17     |
| Abdominal    | 11 (20.4)     | 4 (33.3)               | 18 (39.1)              | .11     |
| Cardiovascular | 6 (11.1) | 0 (0.0)                | 5 (10.9)               | .74     |
| Urinary tract | 3 (5.6)     | 0 (0.0)                | 3 (6.5)                | >.99    |
| CNS          | 2 (3.7)       | 0 (0.0)                | 0 (0.0)                | .60     |
| Skin or soft tissue | 2 (3.7) | 2 (16.7)               | 4 (8.7)                | .21     |
| Other c      | 1 (1.9)       | 0 (0.0)                | 0 (0.0)                | >.99    |
| Unknown      | 54 (100.0)    | 12 (100.0)             | 46 (100.0)             | >.99    |
## eTable 21 continued

| Renal function during the first 24 hours | No AKI (n = 54) | Transient AKI (n = 12) | Persistent AKI (n = 46) | P Value |
|----------------------------------------|-----------------|------------------------|-------------------------|---------|
| Creatinine, µmol/L                      | 79 [57 - 119]   | 145 [102 - 182]*       | 172 [145 - 210]*        | <.001   |
| Urea, mmol/L                            | 7.4 [5.5 - 9.5] | 17.0 [10.4 - 20.0]*    | 13.3 [11.3 - 18.3]*     | <.001   |
| Bicarbonate (minimal), mmol/L            | 21.4 [16.8 - 24.2] | 17.4 [14.3 - 20.1]    | 15.2 [12.8 - 18.9]*     | <.001   |
| Urine output, mL                        | 1790 [1261 - 2966] | 1895 [1153 - 2829] | 700 [277 - 1304]*       | <.001   |

| Outcome | Duration of initial MV, days | 2 [2 - 5] | 4 [2 - 6] | 2 [1 - 3] | .23 |
|---------|------------------------------|-----------|-----------|-----------|-----|
|         | Recurrence of MV             | 1 (1.9)   | 1 (8.3)   | 2 (4.3)   | .32 |
|         | MV-free days                 | 86 [60 - 88] | 86 [16 - 88] | 16 [11 - 87]* | .008 |
|         | Use of RRT                   | 1 (1.9)   | 0 (0.0)   | 14 (30.4)* | <.001 |
|         | RRT-free days                | 90 [67 - 90] | 90 [25 - 90] | 26 [2 - 90]*† | <.001 |

| Complications | None | 51 (94.4) | 9 (75.0) | 41 (89.1) | .12 |
|---------------|------|-----------|----------|-----------|-----|
|               | ICU-acquired AKI | 3 (5.6)  | 1 (8.3)  | 1 (2.2)  | .41 |
|               | ICU-acquired ARDS | 1 (1.9)  | 1 (8.3)  | 2 (4.3)  | .32 |
|               | ICU-acquired infection | 0 (0.0)  | 1 (8.3)  | 4 (8.7)  | .05 |
| ICU length of stay, days | 4 [3 - 7] | 7 [5 - 9] | 3 [3 - 7] | .06 |
| Hospital length of stay, days | 17 [10 - 36] | 17 [12 - 39] | 13 [3 - 30] | .14 |
| ICU-mortality | 7 (13.0) | 2 (16.7) | 20 (43.5)* | .002 |
| 30-day mortality | 10 (18.5) | 4 (33.3) | 22 (47.8)* | .006 |
| 60-day mortality | 13 (24.1) | 4 (33.3) | 23 (50.0)* | .023 |
| 90-day mortality | 15 (27.8) | 4 (33.3) | 25 (54.3)* | .024 |
| 1-year mortality | 23 (42.6) | 6 (50.0) | 28 (60.9) | .19 |
| ICU-free days | 84 [63 - 86] | 83 [13 - 85] | 10 [0 - 84]* | .009 |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson \( \chi^2 \) test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

* Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

* Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

* Other sites of infection: Postoperative wound infections (n=1).

* Between inclusion and day-90.

* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### eTable 22. Baseline characteristics and outcomes of patients admitted to the ICU with septic shock of long duration (≥ 52 hours) and with plasma biomarkers measured upon admission, stratified according to the presence and evolution of acute kidney injury

| No AKI (n = 83) | Transient AKI (n = 16) | Persistent AKI (n = 123) | P Value |
|-----------------|------------------------|--------------------------|---------|
| **Demographics** |                        |                          |         |
| Age, years      | 59 [48 - 69]           | 61 [53 - 71]             | 64 [53 - 73] | .08 |
| Male sex        | 50 (60.2)              | 9 (56.2)                 | 65 (52.8) | .60 |
| Race, white     | 69 (84.1)              | 15 (93.8)                | 113 (92.6) | .12 |
| Medical admission | 63 (75.9)           | 10 (62.5)                | 86 (69.9) | .45 |
| **Chronic comorbidities** |                  |                          |         |
| None            | 22 (26.5)              | 6 (37.5)                 | 32 (26.0) | .62 |
| Cardiovascular compromise | 28 (33.7) | 3 (18.8) | 36 (29.3) | .52 |
| Hypertension    | 21 (25.3)              | 7 (43.8)                 | 34 (27.6) | .31 |
| Diabetes        | 12 (14.5)              | 1 (6.2)                  | 20 (16.3) | .70 |
| Liver cirrhosis | 2 (2.4)                | 0 (0.0)                  | 2 (1.6)   | >.99 |
| Immune compromise | 18 (21.7)              | 1 (6.2)                  | 29 (23.6) | .33 |
| Malignancy      | 26 (31.3)              | 3 (18.8)                 | 28 (22.8) | .32 |
| Charlson comorbidity index | 3 [1 - 5] | 3 [2 - 4] | 3 [2 - 5] | .55 |
| **Chronic medication** |                  |                          |         |
| Diuretics       | 15 (18.1)              | 5 (31.2)                 | 33 (26.8) | .27 |
| ACE inhibitors / ARBs | 14 (16.9) | 4 (25.0) | 38 (30.9) | .07 |
| Calcium-entry blockers | 12 (14.5) | 3 (18.8) | 19 (15.4) | .88 |
| Beta-adrenergic blockers | 16 (19.3) | 6 (37.5) | 24 (19.5) | .23 |
| NSAIDs and Cox II inhibitors | 10 (12.0) | 3 (18.8) | 12 (9.8) | .47 |
| Oral antidiabetic drugs | 9 (10.8) | 0 (0.0) | 18 (14.6) | .26 |
| Corticosteroids | 9 (10.8)               | 0 (0.0)                  | 10 (8.1)  | .44 |
| Antiplatelet drugs | 21 (26.6) | 2 (13.3) | 29 (24.4) | .61 |
| **Severity at time of admission to ICU** |                  |                          |         |
| APACHE IV score | 76 [66 - 94]           | 78 [70 - 89]             | 100 [81 - 118] | <.001 |
| Acute physiology score | 66 [56 - 82] | 65 [56 - 78] | 86 [68 - 105] | <.001 |
| mSOFA score     | 8 [7 - 9]              | 9 [9 - 10]               | 10 [8 - 12] | <.001 |
| Non-renal mSOFA score | 8 [6 - 9] | 8 [8 - 9] | 8 [7 - 10] | .028 |
| Shock            | 83 (100.0)             | 16 (100.0)               | 123 (100.0) | >.99 |
| ARDS             | 33 (39.8)              | 5 (31.2)                 | 53 (43.1) | .66 |
| **Therapy during the first 24h** |                  |                          |         |
| Mechanical ventilation | 80 (96.4) | 16 (100.0) | 112 (91.1) | .23 |
| Vasopressors     | 83 (100.0)             | 16 (100.0)               | 123 (100.0) | >.99 |
| Dose of vasopressors (mg)a | 15.3 [10.1 - 22.0] | 22.7 [17.5 - 40.2] * | 23.3 [12.1 - 39.6] * | <.001 |
| Inotropes        | 9 (10.8)               | 2 (12.5)                 | 33 (26.8) | .013 |
| Dose of inotropes (mg)a | 216.2 [23.4 - 260.4] | 180.7 [161.8 - 225.5] [143.0 - 408.3] | <.001 |
| RRT              | 1 (1.2)                | 0 (0.0)                  | 40 (32.5) | <.001 |
| Nephrotoxic drugs (≥ one) | 45 (54.2) | 11 (68.8) | 91 (74.0) | .014 |
| Aminoglycoside   | 19 (22.9)              | 8 (50.0)                 | 44 (35.8) | .040 |
| Glycopeptide     | 15 (18.1)              | 1 (6.2)                  | 23 (18.7) | .57 |
| Colloid          | 28 (33.7)              | 8 (50.0)                 | 68 (55.3) | <.001 |
| Otherb           | 8 (9.6)                | 0 (0.0)                  | 9 (7.3)   | .53 |
| **Source of infection** |                  |                          |         |
| Pulmonary tract  | 49 (59.0)              | 5 (31.2)                 | 50 (40.7) | .016 |
| Abdominal        | 17 (20.5)              | 8 (50.0)                 | 30 (24.4) | .06 |
| Cardiovascular   | 8 (9.6)                | 0 (0.0)                  | 17 (13.8) | .26 |
| Urinary tract    | 3 (3.6)                | 1 (6.2)                  | 8 (6.5)   | .57 |
| CNS              | 0 (0.0)                | 0 (0.0)                  | 4 (3.3)   | .27 |
| Skin or soft tissue | 4 (4.8)                | 1 (6.2)                  | 9 (7.3)   | .76 |
| Otherc           | 2 (2.4)                | 1 (6.2)                  | 3 (2.4)   | .51 |
| Unknown          | 0 (0.0)                | 0 (0.0)                  | 2 (1.6)   | .58 |
**Table 22 continued**

| Renal function during the first 24 hours | No AKI (n = 83) | Transient AKI (n = 16) | Persistent AKI (n = 123) | P Value |
|----------------------------------------|----------------|------------------------|--------------------------|---------|
| Creatinine, µmol/L                     | 84 [73 - 109]  | 141 [103 - 158]*       | 176 [129 - 227]*         | <.001   |
| Urea, mmol/L                           | 7.1 [5.3 - 10.5]| 12.9 [8.1 - 16.4]*     | 11.9 [8.8 - 17.1]$       | <.001   |
| Bicarbonate (minimal), mmol/L          | 19.7 [17.0 - 22.4]| 18.5 [17.2 - 21.9]     | 16.0 [13.3 - 18.6]$      | <.001   |
| Urine output, mL                       | 1625 [1175 - 2198]| 1523 [1145 - 2361]     | 950 [480 - 1380]*†       | <.001   |
| Outcome                                |                |                        |                          |         |
| Duration of initial MV, days           | 7 [4 - 16]     | 7 [6 - 11]             | 7 [3 - 13]*†             | .84     |
| Recurrence of MV                       | 3 [3.6]        | 2 [12.5]               | 8 [6.5]                  | .26     |
| MV-free days                           | 67 [2 - 84]    | 79 [72 - 83]           | 29 [1 - 79]*†            | .005    |
| Use of RRT†                            | 11 [13.3]      | 0 [0.0]                | 67 [64.5]*               | <.001   |
| RRT-free days                          | 90 [17 - 90]   | 90 [90 - 90]           | 36 [5 - 88]              | <.001   |

**Complications**

| Complications | No AKI (n = 83) | Transient AKI (n = 16) | Persistent AKI (n = 123) | P Value |
|---------------|----------------|------------------------|--------------------------|---------|
| None          | 58 (69.9)      | 12 (75.0)              | 94 (76.4)                | .60     |
| ICU-acquired AKI | 16 (19.3)    | 1 (6.2)                | 8 (6.5)*                 | .015    |
| ICU-acquired ARDS | 6 (7.2)      | 1 (6.2)                | 4 (3.3)                  | .35     |
| ICU-acquired infection | 15 (18.1) | 4 (25.0)               | 23 (18.7)                | .77     |
| ICU length of stay, days               | 9 [6 - 20]    | 10 [8 - 15]            | 10 [6 - 17]              | .93     |
| Hospital length of stay, days          | 27 [13 - 51]  | 32 [22 - 44]           | 22 [9 - 42]              | .10     |
| ICU-mortality                           | 24 (28.9)     | 1 (6.2)                | 54 (43.9)*†              | .002    |
| 30-day mortality                        | 23 (27.7)     | 1 (6.2)                | 54 (43.9)*†              | .002    |
| 60-day mortality                        | 29 (34.9)     | 3 (18.8)               | 64 (52.0)*†              | .007    |
| 90-day mortality                        | 32 (38.6)     | 3 (18.8)               | 70 (56.9)*†              | .002    |
| 1-year mortality                        | 37 (44.6)     | 4 (25.0)               | 80 (65.0)*†              | .001    |

**ICU-free days**

| ICU-free days | No AKI (n = 83) | Transient AKI (n = 16) | Persistent AKI (n = 123) | P Value |
|---------------|----------------|------------------------|--------------------------|---------|
|               | 65 [0 - 82]    | 78 [69 - 81]           | 21 [0 - 78]              | .003    |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson $\chi^2$ test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

* Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

‡ Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

§ Other sites of infection: Infections of bones and joints (n=3), Upper respiratory tract infections (n=2), Viral systemic infections (n=1)

a Between inclusion and day-90.

* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
**eTable 23. Host response biomarkers in patients with septic shock of long duration (≥ 52 hours) during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission**

|                  | Admission                      | Day-2                        | Day 4                        | P Value (group) | P Value (time x group) |
|------------------|-------------------------------|------------------------------|------------------------------|-----------------|------------------------|
|                  | No AKI (n= 83)                | Transient AKI (n= 16)        | Persistent AKI (n= 123)      | No AKI (n= 82)  | Transient AKI (n= 16)  | Persistent AKI (n= 114) | No AKI (n= 70) | Transient AKI (n= 12) | Persistent AKI (n= 96) |                |                        |
| **Inflammatory responses**                  |                               |                              |                              |                 |                        |                          |               |                        |                          |                |                        |
| IL-10 (pg/mL)  | 14.4                          | 42.2                         | 52.9                         | 6.9             | 11.6                  | 20.4                     | 5.3            | 4.0                       | 15.1                     | <0.001       | 0.020                 |
|                | [4.1-57.8]                     | [23.2-176.4]*                | [14.7-260.1]*†               | [2.9-18.0]      | [7.6-33.7]           | [8.9-88.9]*               |               |                           |                           |              |                       |
| IL-6 (pg/mL)   | 475.2                         | 2612.9                       | 1061.4                       | 90.1            | 176.2                 | 276.7                     | 51.7           | 21.7                      | 56.6                     | 0.038        | 0.002                 |
|                | [63.4-2587.9]                  | [212.9-6481.0]               | [152.1-6271.5]               | [27.9-422.6]    | [63.3-214.2]         | [41.5-1416.7]*            |               |                           |                           |              |                       |
| IL-8 (pg/mL)   | 121.5                         | 615.6                        | 575.1                        | 56.7            | 167.0                 | 314.6                     | 46.0           | 55.3                      | 110.4                    | <0.001       | 0.17                  |
|                | [45.2-783.2]                   | [162.9-1078.3]               | [267.7]*                     | [27.1-196.9]    | [93.3-211.5]         | [80.9-1040.5]*            |               |                           |                           |              |                       |
| MMP-8 (ng/mL)  | 2.7                           | 15.0                         | 6.5                          | 2.1             | 6.8                   | 6.3                       | 1.2            | 1.4                       | 4.5                      | <0.001       | 0.45                  |
|                | [1.0-7.1]                      | [6.0-21.8]*                  | [2.0-18.0]*                  | [0.7-7.2]       | [2.4-17.2]           | [2.0-18.3]*               |               |                           |                           |              |                       |
| **Endothelial cell activation**              |                               |                              |                              |                 |                        |                          |               |                           |                           |                |                        |
| Fractalkine (pg/mL)  | 28.2                         | 34.3                         | 55.7                         | 24.4            | 33.5                  | 69.3                     | 25.4           | 26.8                      | 76.0                     | <0.001       | 0.09                  |
|                | [16.6-74.0]                    | [18.2-61.4]                  | [25.7-122.0]*                | [12.9-49.1]     | [23.5-40.5]          | [33.7-142.7]*             |               |                           |                           |              |                       |
| sE-Selectin (ng/mL) | 10.0                         | 21.6                         | 14.7                         | 11.7            | 12.8                  | 13.2                     | 7.8            | 7.3                       | 8.2                      | 0.65         | 0.048                 |
|                | [4.1-24.2]                     | [6.2-51.0]                   | [6.1-30.5]                   | [3.8-22.9]      | [6.5-22.2]           | [5.0-27.2]               |               |                           |                           |              |                       |
| sICAM-1 (ng/mL) | 185.9                         | 232.9                        | 221.6                        | 231.7           | 264.0                 | 277.6                     | 259.3          | 215.7                     | 271.5                    | 0.17         | 0.31                  |
|                | [97.1-308.9]                   | [109.8-395.8]                | [356.5]                      | [110.4-144.7]   | [156.8-400.4]        | [150.1-374.8]            |               |                           |                           |              |                       |
| Angiopoietin-1 (ng/mL) | 2.2                           | 3.5                          | 1.6                          | 1.5             | 1.7                   | 1.0                      | 1.4            | 1.6                       | 0.7                      | 0.004        | 0.80                  |
|                | [0.7-5.7]                      | [1.2-8.5]                    | [0.7-2.8]                    | [0.8-3.7]       | [0.8-4.0]            | [0.6-2.0]*               |               |                           |                           |              |                       |
| Angiopoietin-2 (ng/mL) | 6.2                           | 13.6                         | 15.3                         | 8.6             | 19.3                  | 21.5                     | 6.0            | 7.3                       | 12.3                     | <0.001       | 0.78                  |
|                | [2.9-13.1]                     | [6.7-23.6]                   | [5.8-33.7]*                  | [4.9-17.4]      | [12.4-25.0]*         | [13.5-55.8]*             |               |                           |                           |              |                       |
| ANG-2:ANG-1 (ng/mL) | 2.5                           | 2.4                          | 9.8                          | 8.0             | 10.0                  | 28.1                     | 4.4            | 5.2                       | 17.5                     | <0.001       | 0.99                  |
|                | [0.8-10.3]                     | [0.8-15.4]                   | [3.5-28.7]*                  | [2.0-16.1]      | [4.3-22.9]           | [10.3-66.5]*             |               |                           |                           |              |                       |
### eTable 23 continued

|                      | Admission | Day-2 | Day 4 |
|----------------------|-----------|-------|-------|
|                      | No AKI    | Transient AKI | Persistent AKI | No AKI | Transient AKI | Persistent AKI | No AKI | Transient AKI | Persistent AKI |
|                      | (n=...)   | (n=...) | (n=...) | (n=...) | (n=...) | (n=...) | (n=...) | (n=...) | (n=...) |
| Coagulation activation |          |        |        |          |        |        |          |        |        |
| D-dimer (µg/mL)      | 6.9       | 9.9  | 10.9  | 8.3       | 14.3  | 12.7  | 8.2       | 16.6  | 12.8  |
|                      | [4.4-13.6] | [4.6-15.6] | [4.9-22.1] | [3.8-15.2] | [7.3-17.2] | [5.8-22.6]* | [4.8-18.7] | [11.0-20.1] | [6.9-22.6]* |
| Protein C (ng/mL)    | 110.0     | 86.5 | 109.3 | 115.9     | 88.1  | 110.9 | 130.0     | 109.9  | 109.5 |
|                      | [88.1-143.2] | [77.6-117.6] | [87.8-138.0] | [85.1-138.4] | [65.6-115.0] | [81.6-129.7] | [105.7] | [109.5] | [80.0- ]|
| Antithrombin (ng/mL) | 654.7     | 611.4 | 574.5 | 614.9     | 645.8 | 495.9 | 895.0     | 944.3  | 673.0 |
|                      | [394.2-956.1] | [376.8-1155.2] | [909.1] | [371.0-893.4] | [390.8-895.4] | [365.1-732.8] | [468.2-1374.2] | [644.0-1728.0] | [406.7-926.1]* |
| PT (sec)             | 15.5      | 17.6 | 17.9  | 15.0      | 14.0  | 17.0  | 14.5      | 14.0   | 15.0  |
|                      | [13.9-18.8] | [13.2-20.2] | [14.5-24.7]* | [13.0-17.0] | [12.2-16.8] | [14.0-20.0]* | [13.0-16.2] | [11.0-16.0] | [12.0-17.0] |
|                      | [32.8-53.0] | [32.0-45.0] | [38.0-68.0]* | [33.0-44.0] | [33.0-39.0] | [40.0-59.5]* | [30.0-53.5] | [25.5-28.2] | [34.0-53.0]*|
| aPTT (sec)           | 43.5      | 37.0 | 47.0  | 39.0      | 38.0  | 48.0  | 35.0      | 27.0   | 42.5  |
|                      | [32.8-53.0] | [32.0-45.0] | [38.0-68.0]* | [33.0-44.0] | [33.0-39.0] | [40.0-59.5]* | [30.0-53.5] | [25.5-28.2] | [34.0-53.0]*|
| Platelets (10^9/L)   | 139.0     | 159.5 | 115.0 | 129.0     | 136.5 | 116.0 | 141.0     | 120.0  | 88.0  |
|                      | [94.0-223.5] | [117.2-213.2] | [60.0-192.0]* | [74.0-236.0] | [71.8-181.0] | [45.0-168.0]* | [74.5-225.5] | [78.5-182.0] | [33.0-151.5]* |

**Abbreviations:** ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Data presented as median [interquartile range]

Overall P values are derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn’s post hoc tests of multiple comparisons using rank sums.

* Significant vs no AKI
† Significant vs Transient AKI
eTable 24. Baseline characteristics and outcomes of patients admitted to the ICU with septic shock of long duration (≥ 52 hours) and with blood genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury

| Demographics                                      | No AKI (n = 37) | Transient AKI (n = 13) | Persistent AKI (n = 63) | P Value |
|---------------------------------------------------|----------------|------------------------|-------------------------|---------|
| Age, years                                        | 65 [55 - 70]   | 62 [51 - 71]           | 64 [53 - 72]           | .96     |
| Male sex                                          | 21 (56.8)      | 7 (53.8)               | 30 (47.6)              | .69     |
| Race, white                                       | 30 (83.3)      | 11 (84.6)              | 54 (87.1)              | .86     |
| Medical admission                                 | 27 (73.0)      | 9 (69.2)               | 42 (66.7)              | .88     |
| Chronic comorbidities                             |                |                        |                        |         |
| None                                              | 9 (24.3)       | 4 (30.8)               | 22 (34.9)              | .61     |
| Cardiovascular compromise                         | 12 (32.4)      | 3 (23.1)               | 15 (23.8)              | .62     |
| Hypertension                                      | 12 (32.4)      | 6 (46.2)               | 14 (22.2)              | .16     |
| Diabetes                                          | 9 (24.3)       | 1 (7.7)                | 11 (17.5)              | .44     |
| Liver cirrhosis                                   | 1 (2.7)        | 0 (0.0)                | 0 (0.0)                | .44     |
| Immune compromise                                 | 7 (18.9)       | 2 (15.4)               | 12 (19.0)              | >.99    |
| Malignancy                                        | 16 (43.2)      | 3 (23.1)               | 9 (14.3)               | .005    |
| Charlson comorbidity index                        | 4 [2 - 6]      | 3 [2 - 5]              | 3 [2 - 4]              | .14     |
| Chronic medication                                |                |                        |                        |         |
| Diuretics                                         | 9 (24.3)       | 5 (38.5)               | 19 (30.2)              | .61     |
| ACE inhibitors / ARBs                             | 10 (27.0)      | 3 (23.1)               | 13 (20.6)              | .77     |
| Calcium-entry blockers                            | 10 (27.0)      | 2 (15.4)               | 9 (14.3)               | .28     |
| Beta-adrenergic blockers                          | 11 (29.7)      | 4 (30.8)               | 17 (27.0)              | .91     |
| NSAIDs and Cox II inhibitors                      | 6 (16.2)       | 2 (15.4)               | 5 (7.9)                | .37     |
| Oral antidiabetic drugs                           | 7 (18.9)       | 0 (0.0)                | 10 (15.9)              | .28     |
| Corticosteroids                                   | 4 (10.8)       | 0 (0.0)                | 4 (6.3)                | .57     |
| Antiplatelet drugs                                | 12 (35.3)      | 2 (16.7)               | 14 (22.6)              | .31     |
| Severity at time of admission to ICU              |                |                        |                        |         |
| APACHE IV score                                   | 77 [68 - 92]   | 87 [73 - 96]           | 94 [80 - 114]          | .003    |
| Acute physiology score                            | 66 [54 - 77]   | 70 [62 - 79]           | 84 [66 - 104]          | .003    |
| mSOFA score                                       | 8 [7 - 9]      | 9 [8 - 10]             | 10 [8 - 12]            | <.001   |
| Non-renal mSOFA score                             | 8 [7 - 9]      | 8 [7 - 9]              | 8 [7 - 10]             | .30     |
| Shock                                             | 37 (100.0)     | 13 (100.0)             | 63 (100.0)             | >.99    |
| ARDS                                              | 15 (40.5)      | 5 (38.5)               | 30 (47.6)              | .74     |
| Therapy during the first 24h                       |                |                        |                        |         |
| Mechanical ventilation                            | 37 (100.0)     | 13 (100.0)             | 58 (92.1)              | .24     |
| Vasopressors                                      | 37 (100.0)     | 13 (100.0)             | 63 (100.0)             | >.99    |
| Dose of vasopressors (mg)a                        | 17.5 [9.8 - 23.8] | 24.2 [18.3 - 30.0] | 19.5 [12.5 - 22.3] | .025    |
| Inotropes                                         | 3 [8.1]        | 2 (15.4)               | 15 (23.8)              | .14     |
| Dose of inotropes (mg)a                           | 3.3 [3.1 - 179.9] | 180.7 [161.8 - 221.6] | 221.6 [66.3 - 308.8] | .46     |
| RRT                                               | 0 (0.0)        | 0 (0.0)                | 24 (38.1)†             | <.001   |
| Nephrotoxic drugs (≥ one)                         | 25 (67.6)      | 8 (61.5)               | 52 (82.5)              | .11     |
| Aminoglycoside                                    | 7 (18.9)       | 6 (46.2)               | 28 (44.4)              | .023    |
| Glycopeptide                                      | 8 [21.6]       | 1 (7.7)                | 8 (12.7)               | .44     |
| Colloid                                           | 21 (56.8)      | 7 (53.8)               | 47 (74.6)              | .12     |
| Other a                                          | 2 (5.4)        | 0 (0.0)                | 3 (4.8)                | >.99    |
| Source of infection                               |                |                        |                        |         |
| Pulmonary tract                                   | 24 (64.9)      | 5 (38.5)               | 23 (36.5)              | .18     |
| Abdominal                                         | 6 [16.2]       | 6 (46.2)               | 18 (28.6)              | .10     |
| Cardiovascular                                    | 3 [8.1]        | 0 (0.0)                | 8 (12.7)               | .48     |
| Urinary tract                                     | 1 (2.7)        | 1 (7.7)                | 8 (12.7)               | .25     |
| CNS                                               | 0 (0.0)        | 0 (0.0)                | 1 (1.6)                | >.99    |
| Skin or soft tissue                               | 3 (8.1)        | 0 (0.0)                | 4 (6.3)                | .75     |
| Other c                                          | 0 (0.0)        | 1 (7.7)                | 0 (0.0)                | .12     |
| Unknown                                          | 0 (0.0)        | 0 (0.0)                | 1 (1.6)                | >.99    |
| Renal function during the first 24 hours | No AKI (n = 37) | Transient AKI (n = 13) | Persistent AKI (n = 63) | P Value |
|----------------------------------------|-----------------|------------------------|-------------------------|---------|
| **Creatinine, µmol/L**                 | 90 [75 - 109]   | 144 [125 - 163]^*       | 185 [139 - 248]^*       | <.001 |
| **Urea, mmol/L**                       | 7.8 [5.3 - 11.0] | 14.5 [8.4 - 18.0]^*     | 12.2 [8.6 - 17.4]^*     | <.001 |
| **Bicarbonate (minimal), mmol/L**      | 18.5 [16.6 - 21.7] | 18.2 [17.0 - 22.7]     | 16.0 [13.3 - 18.4]^†     | .001   |
| **Urine output, mL**                   | 1500 [1175 - 2080] | 1450 [1200 - 1665]     | 1005 [549 - 1390]^†      | <.001 |
| **Outcome**                            |                 |                        |                         |        |
| **Duration of initial MV, days**       | 9 [5 - 20]      | 7 [4 - 11]             | 8 [5 - 18]              | .79    |
| **Recurrence of MV**                   | 2 (5.4)         | 2 (15.4)               | 6 (9.5)                 | .51    |
| **MV-free days^d**                     | 62 [4 - 84]     | 78 [31 - 83]           | 53 [2 - 80]             | .14    |
| **Use of RRT**                         | 6 (16.2)        | 1 (7.7)                | 40 (63.5)^†             | <.001 |
| **RRT-free days^e**                    | 90 [13 - 90]    | 90 [87 - 90]           | 63 [4 - 90]^†           | <.001 |
| **Complications^a**                    |                 |                        |                         |        |
| **None**                               | 26 (70.3)       | 10 (76.9)              | 46 (73.0)               | .91    |
| **ICU-acquired AKI**                   | 8 (21.6)        | 1 (7.7)                | 6 (9.5)                 | .22    |
| **ICU-acquired ARDS**                  | 1 (2.7)         | 0 (0.0)                | 1 (1.6)                 | >.99   |
| **ICU-acquired infection**             | 5 (13.5)        | 3 (23.1)               | 13 (20.6)               | .61    |
| **ICU length of stay, days**           | 10 [7 - 25]     | 9 [7 - 13]             | 11 [7 - 21]             | .88    |
| **Hospital length of stay, days**      | 37 [13 - 60]    | 32 [24 - 54]           | 24 [12 - 50]            | .38    |
| **ICU-mortality**                      | 9 (24.3)        | 1 (7.7)                | 25 (39.7)               | .040   |
| **30-day mortality**                   | 10 (27.0)       | 1 (7.7)                | 28 (44.4)               | .019   |
| **60-day mortality**                   | 13 (35.1)       | 3 (23.1)               | 29 (46.0)               | .27    |
| **90-day mortality**                   | 14 (37.8)       | 3 (23.1)               | 31 (49.2)               | .19    |
| **1-year mortality**                   | 17 (45.9)       | 4 (30.8)               | 37 (58.7)               | .16    |
| **ICU-free days^d**                    | 62 [1 - 81]     | 78 [45 - 81]           | 50 [0 - 78]             | .10    |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
* Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.
^ Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.
* Other sites of infection: Infections of bones and joints (n=1).
^ Between inclusion and day-90.
* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
**eTable 25. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis, stratified according to the presence and evolution of acute kidney injury (RIFLE I and F only)**

|                         | No AKI (n = 968) | Transient AKI (n = 46) | Persistent AKI (n = 361) | P Value |
|-------------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**        |                  |                        |                          |         |
| Age, years              | 62 [48 - 71]     | 57 [47 - 71]           | 65 [54 - 73]†‡          | <.001   |
| Male sex                | 606 (62.6)       | 29 (63.0)              | 206 (57.6)               | .25     |
| Race, white             | 847 (88.0)       | 37 (80.4)              | 322 (89.9)               | .15     |
| Medical admission       | 721 (74.5)       | 31 (67.4)              | 267 (74.0)               | .53     |
| **Chronic comorbidities** |                |                        |                          |         |
| None                    | 318 (32.9)       | 17 (37.0)              | 104 (28.8)               | .27     |
| Cardiovascular compromise | 229 (23.7)       | 11 (23.9)              | 90 (24.9)                | .88     |
| Hypertension            | 229 (23.7)       | 13 (28.3)              | 98 (27.1)                | .35     |
| Diabetes                | 159 (16.4)       | 7 (15.2)               | 65 (18.0)                | .76     |
| Liver cirrhosis         | 13 (1.3)         | 2 (4.3)                | 15 (4.2)                 | .004    |
| Immune compromise       | 184 (19.0)       | 5 (10.9)               | 69 (19.1)                | .42     |
| Malignancy              | 200 (20.7)       | 8 (17.4)               | 88 (24.4)                | .28     |
| Charlson comorbidity index | 3 [1 - 5]       | 3 [1 - 5]              | 3 [2 - 5]‡              | <.001   |
| **Chronic medication**  |                  |                        |                          |         |
| Diuretics               | 185 (19.1)       | 11 (23.9)              | 88 (24.4)                | .09     |
| ACE inhibitors / ARBs   | 223 (23.0)       | 8 (17.4)               | 95 (26.3)                | .28     |
| Calcium-entry blockers  | 122 (12.6)       | 6 (13.0)               | 44 (12.2)                | .95     |
| Beta-adrenergic blockers | 222 (22.9)       | 12 (26.1)              | 101 (28.0)               | .15     |
| NSAIDs and Cox II inhibitors | 112 (11.9)   | 5 (10.9)               | 41 (11.4)                | >.99    |
| Oral antidiabetic drugs | 113 (11.7)       | 4 (8.7)                | 47 (13.0)                | .68     |
| Corticosteroids         | 99 (10.2)        | 3 (6.5)                | 31 (8.6)                 | .59     |
| Antiplatelet drugs      | 208 (22.5)       | 9 (20.0)               | 83 (23.7)                | .84     |
| **Severity at time of admission to ICU** | | | | |
| APACHE IV score         | 67 [52 - 85]     | 73 [66 - 82]           | 100 [78 - 124]††        | <.001   |
| Acute physiology score  | 55 [42 - 71]     | 64 [56 - 73]†          | 85 [66 - 109]††         | <.001   |
| mSOFA score             | 5 [3 - 7]        | 7 [5 - 9]              | 10 [8 - 12]†             | <.001   |
| Non-renal mSOFA score   | 5 [3 - 7]        | 7 [4 - 8]              | 8 [6 - 9]†              | <.001   |
| Shock                   | 362 (37.4)       | 31 (67.4)              | 277 (76.7)               | <.001   |
| ARDS                    | 192 (19.8)       | 11 (23.9)              | 109 (30.2)†              | <.001   |
| **Therapy during the first 24h** | | | | |
| Mechanical ventilation  | 773 (79.9)       | 37 (80.4)              | 312 (86.4)†              | .018    |
| Vasopressors            | 503 (52.0)       | 32 (69.6)              | 310 (85.9)†              | <.001   |
| Dose of vasopressors (mg)a | 5.8 [2.0 - 13.3] | 10.0 [4.5 - 21.8]†         | 17.6 [6.1 - 37.0]†        | <.001   |
| Inotropes               | 40 (4.1)         | 5 (10.9)               | 65 (18.0)                | <.001   |
| Dose of inotropes (mg)a | 151.3 [46.7 - 82.9] | 23 [50.0] | 193.9 [64.8 - 356.9] | .30     |
| RRT                     | 6 (0.6)          | 2 (4.3)                | 96 (26.7)†              | <.001   |
| Nephrotoxic drugs (≥ one) | 379 (39.2)       | 23 (50.0)              | 220 (60.9)               | <.001   |
| Aminoglycoside          | 128 (13.2)       | 11 (23.9)              | 105 (29.1)               | <.001   |
| Glycopeptide            | 106 (11.0)       | 3 (6.5)                | 62 (17.2)                | .005    |
| Colloid                 | 163 (16.8)       | 11 (23.9)              | 144 (39.9)               | <.001   |
| Other†                  | 94 (9.7)         | 5 (10.9)               | 28 (7.8)                 | .47     |
| **Source of infection** |                  |                        |                          |         |
| Pulmonary tract         | 562 (58.1)       | 21 (45.7)              | 127 (35.2)†              | <.001   |
| Abdominal               | 134 (13.8)       | 13 (28.3)              | 97 (26.9)†               | <.001   |
| Cardiovascular          | 70 (7.2)         | 3 (6.5)                | 45 (12.5)§               | .011    |
| Urinary tract           | 43 (4.4)         | 2 (4.3)                | 39 (10.8)§               | <.001   |
| CNS                     | 56 (5.8)         | 3 (6.5)                | 7 (1.9)§                 | .005    |
| Skin or soft tissue     | 22 (2.3)         | 2 (4.3)                | 21 (5.8)§                | .005    |
| Otherb                  | 78 (8.1)         | 2 (4.3)                | 16 (4.4)                 | .05     |
| Unknown                 | 3 (0.3)          | 0 (0.0)                | 9 (2.5)§                 | .002    |
eTable 25 continued

| Renal function during the first 24 hours | No AKI (n = 968) | Transient AKI (n = 46) | Persistent AKI (n = 361) | P Value |
|----------------------------------------|-----------------|-----------------------|--------------------------|---------|
| Creatinine, µmol/L                     | 79 [60 - 102]   | 133 [91 - 206]*      | 198 [141 - 263]*         | <.001   |
| Urea, mmol/L                           | 6.7 [4.6 - 9.9] | 14.2 [8.2 - 17.7]*   | 14.0 [9.8 - 20.8]*       | <.001   |
| Bicarbonate (minimal), mmol/L          | 22.3 [19.1 - 25.9] | 18.2 [16.1 - 21.4]* | 15.8 [12.9 - 19.1]*      | <.001   |
| Urine output, mL                       | 1900 [1303 - 2815] | 1505 [1055 - 2840]  | 811 [335 - 1480]*        | <.001   |
| Outcome                                |                 |                       |                          |         |
| Duration of initial MV, days           | 2 [1 - 5]       | 2 [1 - 7]             | 3 [1 - 8]*               | <.001   |
| Recurrence of MV                       | 24 (2.5)        | 2 (4.3)               | 21 (5.8)*                | .011    |
| MV-free days†                         | 86 [46 - 89]    | 85 [30 - 88]          | 23 [1 - 84]*             | <.001   |
| Use of RRT                             | 25 (2.6)        | 3 (6.5)               | 147 (40.7)*              | <.001   |
| RRT-free days†                         | 90 [59 - 90]    | 90 [39 - 90]          | 34 [3 - 90]*             | <.001   |
| Complications†                         |                 |                       |                          |         |
| None                                   | 870 (89.9)      | 40 (87.0)             | 306 (84.8)*              | .31     |
| ICU-acquired AKI                       | 57 (5.9)        | 1 (2.2)               | 11 (3.0)                 | .08     |
| ICU-acquired ARDS                      | 20 (2.1)        | 2 (4.3)               | 9 (2.5)                  | .34     |
| ICU-acquired infection                 | 47 (4.9)        | 4 (8.7)               | 45 (12.5)*               | <.001   |
| ICU length of stay, days               | 4 [2 - 8]       | 6 [3 - 9]*            | 5 [3 - 12]*              | <.001   |
| ICU-mortality                          | 109 (11.3)      | 5 (10.9)              | 154 (42.7)*              | <.001   |
| 30-day mortality                      | 197 (20.4)      | 9 (19.6)              | 171 (47.4)*              | <.001   |
| 60-day mortality                      | 245 (25.3)      | 14 (30.4)             | 189 (52.4)*              | <.001   |
| 90-day mortality                      | 274 (28.3)      | 15 (32.6)             | 202 (56.0)*              | <.001   |
| 1-year mortality                      | 365 (37.7)      | 19 (41.3)             | 220 (60.9)*              | <.001   |
| ICU-free days‡                         | 84 [45 - 87]    | 82 [27 - 86]          | 23 [0 - 82]*             | <.001   |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
+a Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine in the first 24 hours.
+b Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.
+c Other sites of infection: Infections of bones and joints (n=17), Oral infections (n=7), Postoperative wound infections (n=20), Upper respiratory tract infections (n=20), Viral systemic infections (n=6), Endometritis (n=4), Other (n=22).
+d Between inclusion and day-90.
* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
| Demographics | No AKI (n = 497) | Transient AKI (n = 26) | Persistent AKI (n = 238) | P Value |
|--------------|-----------------|------------------------|--------------------------|---------|
| Age, years   | 61 [48 - 70]    | 57 [48 - 70]           | 63 [53 - 72]             | .018    |
| Male sex     | 306 (61.6)      | 15 (57.7)              | 130 (54.6)               | .19     |
| Race, white  | 426 (85.9)      | 20 (76.9)              | 208 (88.6)               | .21     |
| Medical admission | 371 (74.6) | 16 (61.5)              | 178 (74.8)               | .33     |
| Chronic comorbidities | | | | |
| None         | 159 (32.0)      | 11 (42.3)              | 66 (27.7)                | .23     |
| Cardiovascular compromise | 114 (22.9) | 6 (23.1)               | 57 (23.9)                | .96     |
| Hypertension | 111 (22.3)      | 9 (34.6)               | 53 (22.3)                | .34     |
| Diabetes     | 78 (15.7)       | 3 (11.5)               | 38 (16.0)                | .91     |
| Liver cirrhosis | 10 (2.0)   | 0 (0.0)                | 0 (0.0)                  | .22     |
| Immune compromise | 109 (21.9) | 1 (3.8)                | 52 (21.8)                | .06     |
| Malignancy   | 105 (21.1)      | 3 (11.5)               | 62 (26.1)                | .15     |
| Charlson comorbidity index | 3 (1 - 5) | 2 [0 - 3]              | 3 [2 - 5]                | .029    |
| Chronic medication | | | | |
| Diuretics    | 90 (18.1)       | 8 (30.8)               | 59 (24.8)                | .043    |
| ACE inhibitors / ARBs | 101 (20.3) | 6 (23.1)               | 63 (26.5)                | .17     |
| Calcium-entry blockers | 58 (11.7) | 5 (19.2)               | 24 (10.1)                | .32     |
| Beta-adrenergic blockers | 105 (21.1) | 6 (23.1)               | 59 (24.8)                | .52     |
| NSAIDs and Cox II inhibitors | 61 (12.3) | 4 (15.4)               | 32 (13.4)                | .73     |
| Oral antidiabetic drugs | 50 (10.1) | 2 (7.7)                | 29 (12.2)                | .69     |
| Corticosteroids | 62 (12.5) | 1 (3.8)                | 21 (8.8)                 | .22     |
| Antiplatelet drugs | 101 (21.7) | 4 (16.0)               | 56 (24.3)                | .59     |
| Severity at time of admission to ICU | | | | |
| APACHE IV score | 69 [54 - 88] | 74 [66 - 81]            | 100 [79 - 121]           | <.001   |
| Acute physiology score | 57 [44 - 71] | 64 [57 - 72]           | 85 [66 - 108]            | <.001   |
| mSOFA score | 6 [4 - 8]       | 8 [6 - 9]              | 10 [8 - 13]              | <.001   |
| Non-renal mSOFA score | 6 [4 - 7] | 6 [4 - 8]              | 8 [7 - 10]               | <.001   |
| Shock | 209 (42.1) | 16 (61.5)              | 186 (78.2)               | <.001   |
| ARDS | 144 (29.0) | 8 (30.8)               | 87 (36.6)                | .12     |
| Therapy during the first 24h | | | | |
| Mechanical ventilation | 427 (85.9) | 20 (76.9)              | 207 (87.0)               | .37     |
| Vasopressors | 295 (59.4) | 16 (61.5)              | 208 (87.4)               | <.001   |
| Dose of vasopressors (mg)a | 5.9 [2.2 - 13.9] | 11.3 [4.3 - 18.3]   | 18.9 [6.8 - 40.0]        | <.001   |
| Inotropes | 16 (3.2)       | 2 (7.7)                | 38 (16.0)                | <.001   |
| Dose of inotropes (mg)a | 159.2 [44.4 - 281.5] | 566.5 [392.4 - 740.6] | 232.4 [100.1 - 395.5] | .20     |
| RRT | 4 (0.8)        | 2 (7.7)                | 73 (30.8)                | <.001   |
| Nephrotoxic drugs (≥ one) | 223 (44.9) | 11 (42.3)              | 162 (66.1)               | <.001   |
| Aminoglycoside | 86 (17.3) | 7 (26.9)               | 76 (31.9)                | <.001   |
| Glycopeptide | 60 (12.1) | 1 (3.8)                | 48 (20.2)                | .005    |
| Colloid | 110 (22.1) | 7 (26.9)               | 104 (43.7)               | <.001   |
| Otherb | 42 (8.5) | 1 (3.8)                | 22 (9.2)                 | .80     |
| Source of infection | | | | |
| Pulmonary tract | 298 (60.0) | 10 (38.5)              | 87 (36.6)                | <.001   |
| Abdominal | 77 (15.5) | 8 (30.8)               | 60 (25.2)                | .002    |
| Cardiovascular | 48 (9.7) | 3 (11.5)               | 29 (12.2)                | .50     |
| Urinary tract | 20 (4.0) | 2 (7.7)                | 25 (10.5)                | .003    |
| CNS | 22 (4.4) | 1 (3.8)                | 5 (2.1)                  | .25     |
| Skin or soft tissue | 13 (2.6) | 2 (7.7)                | 19 (8.0)                 | .003    |
| Otherc | 19 (3.8) | 0 (0.0)                | 8 (3.4)                  | .87     |
| Unknown | 0 (0.0) | 0 (0.0)                | 5 (2.1)                  | .007    |
### eTable 26 continued

| Renal function during the first 24 hours | No AKI (n = 497) | Transient AKI (n = 26) | Persistent AKI (n = 238) | P Value |
|----------------------------------------|-----------------|------------------------|--------------------------|---------|
| Creatinine, µmol/L                     | 79 [61 - 105]   | 133 [92 - 211]*        | 198 [140 - 260]*         | <.001   |
| Urea, mmol/L                           | 6.9 [4.7 - 10.1]| 11.0 [8.2 - 17.3]*     | 13.9 [9.6 - 20.6]*       | <.001   |
| Bicarbonate (minimal), mmol/L          | 22.1 [18.9 - 25.8]| 18.3 [16.6 - 21.4]*     | 15.8 [13.0 - 18.6]*      | <.001   |
| Urine output, mL                       | 1820 [1315 - 2750]| 1665 [1170 - 2840]      | 893 [391 - 1464]*        | <.001   |

| Outcome                                |                  |                        |                          |         |
|----------------------------------------|-----------------|------------------------|--------------------------|---------|
| Duration of initial MV, days           | 2 [1 - 7]       | 2 [2 - 6]              | 3 [2 - 9]                | .07     |
| Recurrence of MV                       | 13 (2.6)        | 1 (3.8)                | 14 (5.9)                 | .06     |
| MV-free days                           | 84 [29 - 88]    | 85 [67 - 88]           | 23 [2 - 84]*†            | <.001   |
| Use of RRT                             | 18 (3.6)        | 3 (11.5)               | 106 (45.4)*†             | <.001   |
| RRT-free days                          | 90 [44 - 90]    | 90 [89 - 90]           | 39 [3 - 90]*†            | <.001   |

| Complications                          |                  |                        |                          |         |
|----------------------------------------|-----------------|------------------------|--------------------------|---------|
| None                                   | 430 (86.5)      | 21 (80.8)              | 201 (84.5)               | .51     |
| ICU-acquired AKI                       | 41 (8.2)        | 1 (3.8)                | 10 (4.2)                 | .10     |
| ICU-acquired ARDS                      | 15 (3.0)        | 1 (3.8)                | 7 (2.9)                  | .85     |
| ICU-acquired infection                 | 32 (6.4)        | 4 (15.4)               | 29 (12.2)*               | .011    |
| ICU length of stay, days               | 5 [3 - 9]       | 7 [3 - 11]             | 6 [3 - 12]               | .012    |
| Hospital length of stay, days          | 17 [10 - 33]    | 23 [15 - 40]           | 15 [5 - 34]              | .007    |
| ICU-mortality                          | 64 (12.9)       | 2 (7.7)                | 98 (41.2)*†              | <.001   |
| 30-day mortality                       | 107 (21.5)      | 3 (11.5)               | 110 (46.2)*†             | <.001   |
| 60-day mortality                       | 139 (28.0)      | 6 (23.1)               | 123 (51.7)*†             | <.001   |
| 90-day mortality                       | 157 (31.6)      | 6 (23.1)               | 132 (55.5)*†             | <.001   |
| 1-year mortality                       | 202 (40.6)      | 8 (30.8)               | 143 (60.1)*†             | <.001   |
| ICU-free days                          | 82 [33 - 86]    | 83 [67 - 87]           | 29 [0 - 81]*†            | <.001   |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

a Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

b Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

c Other sites of infection: Infections of bones and joints (n=7), Oral infections (n=2), Postoperative wound infections (n=4), Upper respiratory tract infections (n=7), Viral systemic infections (n=4), Other (n=3).

d Between inclusion and day-90.

e Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### eTable 27. Host response biomarkers in patients with sepsis during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission (RIFLE I and F only)

|                       | Admission       | Day-2          | Day 4           | P Value (group) | P Value (time x group) |
|-----------------------|-----------------|----------------|-----------------|-----------------|------------------------|
|                       | No AKI (n= 497) | Transient AKI (n= 26) | Persistent AKI (n= 238) | No AKI (n= 374) | Transient AKI (n= 26) | Persistent AKI (n= 178) | No AKI (n= 242) | Transient AKI (n= 14) | Persistent AKI (n= 128) |
| **Inflammatory responses** |                 |                |                 |                 |                       |                       |                 |                       |                     |
| IL-10 (pg/mL)         | 7.2             | 26.1           | 52.2            | 4.3             | 7.8                    | 21.0                   | 3.5             | 4.4                    | 15.1               | <0.001     | <0.001     |
|                       | [3.0-21.1]      | [13.6-51.5]*   | [14.0-246.7]*   | [2.0-10.0]      | [3.7-14.4]             | [8.1-81.8]*†           | [1.8-8.0]      | [2.8-5.5]              | [5.4-35.6]*†        | <0.001     | <0.001     |
| IL-6 (pg/mL)          | 102.0           | 255.0          | 586.5           | 44.2            | 124.5                  | 129.2                  | 27.0            | 25.6                   | 59.3               | <0.001     | <0.001     |
|                       | [27.1-474.5]    | [48.3-780.1]   | [96.5-5739.9]*† | [15.1-149.5]    | [42.8-198.0]*†        | [40.2-966.2]*†         | [10.7-108.1]   | [11.2-55.7]            | [139.0]*†          | <0.001     | <0.001     |
| IL-8 (pg/mL)          | 61.5            | 205.5          | 431.0           | 32.6            | 124.1                  | 185.4                  | 29.2            | 64.4                   | 116.1              | <0.001     | 0.001      |
|                       | [24.2-182.7]    | [45.5-435.5]*  | [110.2-2399.4]* | [15.9-87.9]     | [54.4-184.3]*†        | [70.3-760.8]*†         | [13.8-86.1]    | [38.6-136.1]           | [62.9-273.3]*†     | <0.001     | 0.001      |
| MMP-8 (ng/mL)         | 2.0             | 7.1            | 6.4             | 1.5             | 2.8                    | 4.5                    | 1.0             | 1.3                    | 3.1                | <0.001     | 0.31       |
|                       | [0.6-5.8]       | [2.5-14.6]*    | [1.8-19.8]*     | [0.5-3.9]       | [1.1-5.5]*             | [1.2-15.5]*           | [0.4-2.1]       | [0.5-1.7]              | [0.8-8.5]*†        | <0.001     | 0.17       |
| **Endothelial cell activation** |               |                |                 |                 |                       |                       |                 |                       |                    |
| Fractalkine (pg/mL)   | 19.9            | 21.7           | 52.7            | 16.7            | 20.2                   | 55.7                   | 18.4            | 33.3                   | 59.0               | <0.001     | 0.022      |
|                       | [12.8-38.8]     | [13.9-49.5]    | [23.7-115.3]*†  | [12.8-34.1]     | [11.3-54.8]            | [25.9-127.8]*†         | [12.8-44.9]    | [15.0-49.9]            | [142.0]*†          | <0.001     | 0.022      |
| sE-Selectin (ng/mL)   | 8.8             | 11.9           | 14.3            | 8.9             | 8.6                    | 12.1                   | 7.6             | 5.3                    | 9.7                | <0.001     | 0.017      |
|                       | [4.2-21.2]      | [5.3-26.0]     | [5.9-34.7]*     | [4.0-17.3]      | [4.7-20.8]             | [4.7-24.7]*†          | [3.6-15.1]     | [4.1-14.6]             | [4.7-19.0]         | <0.001     | 0.028      |
| sICAM-1 (ng/mL)       | 155.7           | 161.2          | 230.4           | 169.4           | 147.2                  | 276.9                  | 203.6           | 163.1                  | 273.8              | <0.001     | 0.001      |
|                       | [88.2-286.5]    | [105.7-234.6]  | [140.4-395.6]*  | [105.3-300.3]   | [109.8-292.0]          | [148.7-458.2]*†        | [109.8-335.5]  | [105.5-254.6]          | [175.3-430.6]*†    | <0.001     | 0.28       |
| Angiopoietin-1 (ng/mL)| 2.6             | 3.6            | 3.8             | 2.0             | 2.2                    | 2.1                    | 2.1             | 1.8                    | 0.8                | <0.001     | 0.026      |
|                       | [1.0-6.2]       | [1.3-7.2]      | [0.7-3.7]*†     | [0.5-5.3]       | [0.8-3.2]             | [0.6-1.9]*†           | [0.9-4.7]      | [1.0-2.3]              | [0.5-2.3]*†        | <0.001     | 0.026      |
| Angiopoietin-2 (ng/mL)| 4.7             | 7.0            | 13.6            | 5.5             | 7.1                    | 18.3                   | 4.0             | 4.6                    | 9.6                | <0.001     | 0.28       |
|                       | [2.2-9.3]       | [3.2-15.7]     | [6.0-30.4]*†    | [2.6-10.3]      | [3.8-13.1]             | [9.3-44.5]*†‡         | [2.0-9.4]      | [3.1-7.8]              | [4.7-25.1]*†       | <0.001     | 0.28       |
| ANG-2:ANG-1 (ng/mL)   | 1.7             | 2.2            | 9.6             | 2.3             | 4.9                    | 22.4                   | 1.7             | 3.6                    | 14.5               | <0.001     | 0.001      |
|                       | [0.5-6.1]       | [0.6-5.5]      | [2.5-30.8]*†    | [0.6-9.2]       | [2.1-13.8]             | [6.6-56.6]*†          | [0.5-7.6]       | [2.7-5.9]              | [4.2-37.1]*†       | <0.001     | 0.99       |
| Coagulation activation | Admission | Day-2 | Day 4 |
|------------------------|-----------|-------|-------|
|                        | No AKI    | Transient AKI | Persistent AKI | No AKI    | Transient AKI | Persistent AKI | No AKI    | Transient AKI | Persistent AKI |
| D-dimer (µg/mL)        | 7.2       | 7.2   | 12.1   | 6.3       | 9.3         | 14.4         | 8.3       | 6.9         | 13.6         | <0.001   0.66 |
|                        | [3.3-15.4]| [2.1-14.1]| [5.6-23.8]| [3.3-12.7]| [4.6-14.6]| [6.7-25.1]| [4.5-16.0]| [2.8-19.2]| [7.1-24.2]| <0.001 0.66 |
| Protein C (ng/mL)      | 122.7     | 110.8 | 111.1  | 125.3     | 107.9       | 112.2        | 141.3     | 129.9       | 122.3       | 107.0    79.5 |
|                        | [90.0-159.0]| [77.9-157.6]| [86.1-142.6]| [94.8-169.1]| [67.5-126.0]| [83.6-140.1]| [100.8]| [122.3]| [107.0]| <0.001 0.019 |
| Antithrombin (ng/mL)   | 773.7     | 621.0 | 615.3  | 778.7     | 780.6       | 568.8        | 934.4     | 1070.6      | 723.1        | <0.001 0.038 |
|                        | [539.5-1111.2]| [494.0-977.4]| [394.5-929.9]| [490.9-1130.6]| [515.9-1033.7]| [399.6-894.1]| [585.7-1446.2]| [831.8-1808.3]| [467.6-1144.7]| <0.001 0.038 |
| PT (sec)               | 14.8      | 13.6  | 17.4   | 14.0      | 13.0        | 16.0         | 14.0      | 12.0        | 14.0         | <0.001 <0.001 |
|                        | [12.5-17.3]| [12.5-16.6]| [14.2-22.8]| [12.0-16.0]| [12.0-14.8]| [13.0-19.8]| [12.0-15.0]| [11.0-14.0]| [12.0-17.0]| <0.001 <0.001 |
| aPTT (sec)             | 34.0      | 37.5  | 45.0   | 33.0      | 36.0        | 46.0         | 36.0      | 27.0        | 40.0         | <0.001 0.07  |
|                        | [29.0-44.0]| [29.8-48.8]| [36.0-64.0]| [29.0-43.0]| [33.5-38.0]| [36.0-59.0]| [26.0-45.8]| [27.0-35.0]| [33.0-49.0]| <0.001 0.04  |
| Platelets (10^9/L)     | 181.5     | 158.5 | 111.5  | 182.0     | 141.5       | 116.0        | 196.0     | 159.5       | 85.0         | <0.001 0.04  |
|                        | [123.0-261.2]| [98.0-246.0]| [45.2-112.0]| [90.8-223.0]| [44.5-179.5]| [274.5]| [87.5-179.0]| [31.2-174.0]| <0.001 0.04  |

Abbreviations: ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Data presented as median [interquartile range]

Overall P values are derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn’s post hoc tests of multiple comparisons using rank sums.

* Significant vs no AKI
† Significant vs Transient AKI
Baseline characteristics and outcomes of patients admitted to the ICU with sepsis and with blood genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury (RIFLE I and F only)

|                      | No AKI (n = 225) | Transient AKI (n = 11) | Persistent AKI (n = 102) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**     |                  |                        |                          |         |
| Age, years           | 63 [49 - 70]     | 59 [49 - 71]           | 65 [56 - 72]             | .25     |
| Male sex             | 130 (57.8)       | 4 (36.4)               | 56 (54.9)                | .35     |
| Race, white          | 184 (82.8)       | 10 (90.9)              | 87 (87.0)                | .59     |
| Medical admission    | 166 (73.8)       | 7 (63.6)               | 70 (68.6)                | .50     |
| **Chronic comorbidities** |            |                        |                          |         |
| None                 | 74 (32.9)        | 4 (36.4)               | 33 (32.4)                | .95     |
| Cardiovascular       | 47 (20.9)        | 2 (18.2)               | 23 (22.5)                | .93     |
| Hypertension         | 50 (22.2)        | 3 (27.3)               | 24 (23.5)                | .82     |
| Diabetes             | 37 (16.4)        | 1 (9.1)                | 20 (19.6)                | .69     |
| Liver cirrhosis      | 4 (1.8)          | 0 (0.0)                | 3 (2.9)                  | .75     |
| Immune compromise    | 51 (22.7)        | 1 (9.1)                | 19 (18.6)                | .52     |
| Malignancy           | 50 (22.2)        | 2 (18.2)               | 19 (18.6)                | .84     |
| Charlson comorbidity index | 3 [1 - 5] | 2 [1 - 4] | 3 [2 - 4] | .56 |
| **Chronic medication** |               |                        |                          |         |
| Diuretics            | 44 (19.6)        | 6 (54.5)               | 27 (26.5)*               | .018    |
| ACE inhibitors / ARBs| 46 (20.4)        | 3 (27.3)               | 30 (29.4)                | .19     |
| Calcium-entry blockers| 29 (12.9)       | 4 (36.4)               | 11 (10.8)                | .08     |
| Betas-adrnergic blockers | 52 (23.1)     | 4 (36.4)               | 34 (33.3)                | .10     |
| NSAIDs and Cox II inhibitors | 34 (15.1) | 3 (27.3) | 9 (8.8) | .11     |
| Oral antidilatic drugs | 20 (8.9)        | 1 (9.1)                | 16 (15.7)                | .18     |
| Corticosteroids      | 31 (13.8)        | 1 (9.1)                | 6 (5.9)                  | .08     |
| Antiplaetelet drugs  | 46 (22.9)        | 1 (10.0)               | 27 (27.3)                | .49     |
| **Severity at time of admission to ICU** |        |                        |                          |         |
| APACHE IV score      | 71 [57 - 89]     | 75 [72 - 84]           | 97 [78 - 118]*           | <.001   |
| Acute physiology score | 59 [47 - 72]   | 69 [60 - 70]*          | 83 [65 - 107]*           | <.001   |
| mSOFA score          | 6 [4 - 8]        | 9 [6 - 10]*            | 10 [8 - 13]*             | <.001   |
| Non-renal mSOFA score | 6 [4 - 7]       | 9 [6 - 9]*             | 8 [7 - 10]*              | <.001   |
| Shock                | 91 (40.4)        | 8 (72.7)*              | 87 (85.3)*               | <.001   |
| ARDS                 | 63 (28.0)        | 4 (36.4)               | 43 (42.2)*               | .035    |
| **Therapy during the first 24h** |            |                        |                          |         |
| Mechanical ventilation | 194 (86.2)      | 8 (72.7)               | 93 (91.2)                | .12     |
| Vasopressors         | 130 (57.8)       | 8 (72.7)*              | 93 (91.2)*               | <.001   |
| Dose of vasopressors (mg)* | 5.9 [2.3 - 14.4] | 15.1 [2.8 - 26.9] | 19.5 [10.5 - 45.0]* | <.001   |
| Inotropes            | 9 (4.0)          | 2 (18.2)               | 20 (19.6)*               | <.001   |
| Dose of inotropes (mg)* | 150.2 [75.5 - 344.8] | 566.5 [392.4 - 740.6] | 159.2 [61.7 - 268.4] | .44     |
| RRT                  | 0 (0.0)          | 0 (0.0)                | 35 (34.3)*               | <.001   |
| Nephrotoxic drugs (≥ one) | 115 (51.1)      | 7 (63.6)               | 86 (84.3)*               | <.001   |
| Aminoglycoside       | 44 (19.6)        | 4 (36.4)               | 41 (40.2)*               | <.001   |
| Glycopeptide         | 25 (11.1)        | 1 (9.1)                | 11 (10.8)                | .99     |
| Colloid              | 72 (32.0)        | 5 (45.5)               | 70 (68.6)*               | <.001   |
| Other*               | 11 (4.9)         | 1 (9.1)                | 8 (7.8)                  | .35     |
| **Source of infection** |                     |                          |                          |         |
| Pulmonary tract      | 130 (57.8)       | 4 (36.4)               | 39 (38.2)*               | .003    |
| Abdominal            | 42 (18.7)        | 3 (27.3)*              | 34 (33.3)*               | .013    |
| Cardiovascular       | 23 (10.2)        | 1 (9.1)                | 11 (10.8)                | .94     |
| Urinary tract        | 12 (5.3)         | 1 (9.1)                | 9 (8.8)                  | .32     |
| CNS                  | 8 (3.6)          | 0 (0.0)                | 1 (1.0)                  | .47     |
| Skin or soft tissue  | 8 (3.6)          | 2 (18.2)               | 8 (7.8)                  | .044    |
| Other*               | 2 (0.9)          | 0 (0.0)                | 0 (0.0)                  | .99     |
| Unknown              | 225 (100.0)      | 11 (100.0)             | 102 (100.0)              | >.99    |
### Renal function during the first 24 hours

|                      | No AKI (n = 225) | Transient AKI (n = 11) | Persistent AKI (n = 102) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| **Creatinine, µmol/L** | 80 [61 - 105]    | 125 [85 - 195]*        | 191 [141 - 253]*         | <.001   |
| **Urea, mmol/L**      | 7.1 [5.1 - 9.9]  | 11.2 [7.6 - 17.6]*     | 12.4 [9.2 - 17.8]*       | <.001   |
| **Bicarbonate (minimal), mmol/L** | 21.7 [18.2 - 26.2] | 17.3 [15.0 - 21.9]* | 16.1 [13.6 - 18.7]* | <.001   |
| **Urine output, mL**  | 1780 [1265 - 2810] | 1800 [1613 - 3841] | 930 [354 - 1318]†       | <.001   |

### Outcome

|                      | No AKI (n = 225) | Transient AKI (n = 11) | Persistent AKI (n = 102) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| **Duration of initial MV, days** | 3 [1 - 7] | 4 [1 - 7] | 5 [2 - 10]* | .028   |
| **Recurrence of MV**  | 7 (3.1) | 0 (0.0) | 7 (6.9) | .27    |
| **MV-free days**      | 83 [39 - 88] | 84 [77 - 87] | 18 [1 - 81]† | <.001   |
| **Use of RRT**        | 7 (3.1) | 0 (0.0) | 53 (52.0)*† | <.001   |
| **RRT-free days**     | 90 [55 - 90] | 90 [90 - 90] | 24 [2 - 90] | <.001   |

### Complications

|                      | No AKI (n = 225) | Transient AKI (n = 11) | Persistent AKI (n = 102) | P Value |
|----------------------|------------------|------------------------|--------------------------|---------|
| **ICU length of stay, days** | 5 [3 - 9] | 7 [7 - 11]* | 8 [4 - 14]* | .002   |
| **Hospital length of stay, days** | 18 [10 - 36] | 22 [18 - 35] | 20 [5 - 45] | .62    |
| **ICU-mortality**     | 24 (10.7) | 1 (9.1) | 42 (41.2)* | <.001   |
| **30-day mortality**  | 45 (20.0) | 1 (9.1) | 51 (50.0)*† | <.001   |
| **60-day mortality**  | 59 (26.2) | 2 (18.2) | 54 (52.9)* | <.001   |
| **90-day mortality**  | 65 (28.9) | 2 (18.2) | 58 (56.9)* | <.001   |
| **ICU-free days**     | 81 [39 - 87] | 82 [75 - 84] | 14 [0 - 79]* | <.001   |

**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson $\chi^2$ test or the Fisher’s exact test when appropriate. $P$ value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

‡ Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

§ Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

¶ Other sites of infection: Oral infections (n=1), Postoperative wound infections (n=1)

‡‡ Between inclusion and day-90.

* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### eTable 29. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis, stratified according to the presence and evolution of acute kidney injury based on a 72-hour cutoff

| Source of infection                  | No AKI (n = 426) | AKI (n = 482) | P Value |
|--------------------------------------|------------------|---------------|---------|
| Pulmonary tract                      | 562 (58.1)       | 75 (49.7)     | <.001   |
| Abdominal                            | 134 (13.8)       | 38 (25.2)     | <.001   |
| Cardiovascular                       | 70 (7.2)         | 12 (7.9)      | .001    |
| Urinary tract                        | 43 (4.4)         | 8 (5.3)       | .001    |
| CNS                                  | 56 (5.8)         | 6 (4.0)       | .007    |
| Skin or soft tissue                  | 22 (2.3)         | 5 (3.3)       | .003    |
| Other                                | 68 (7.1)         | 12 (8.2)      | <.001   |
| Unknown                              | 3 (0.3)          | 0 (0.0)       | <.001   |

#### Demographics

|                        | No AKI (n = 968) | AKI (n = 151) | P Value |
|------------------------|------------------|---------------|---------|
| Age, years             | 62 [48 - 71]     | 64 [51 - 73]  | <.001   |
| Male sex               | 606 (62.6)       | 87 (57.6)     | .23     |
| Race, white            | 848 (86.8)       | 133 (88.1)    | .65     |
| Medical admission      | 721 (74.5)       | 111 (73.5)    | .52     |

#### Chronic comorbidities

|                        | No AKI (n = 968) | AKI (n = 151) | P Value |
|------------------------|------------------|---------------|---------|
| Malignancy             | 131 (5.3)        | 17 (11.3)     | <.001   |
| Immune compromise      | 184 (19.0)       | 29 (19.2)     | .98     |
| Malignancy             | 200 (20.7)       | 32 (21.2)     | .39     |
| Charlson comorbidity index | 3 [1 - 5]     | 3 [2 - 5]     | <.001   |

#### Chronic medication

|                        | No AKI (n = 968) | AKI (n = 151) | P Value |
|------------------------|------------------|---------------|---------|
| Vasopressors           | 503 (52.0)       | 120 (79.5)    | <.001   |
| Non-renal mSOFA score  | 5 [3 - 7]        | 7 [5 - 8]     | <.001   |
| Shock                  | 362 (37.4)       | 103 (68.2)    | <.001   |
| ARDS                   | 192 (19.8)       | 40 (25.6)     | <.001   |

#### Severity at time of admission to ICU

|                        | No AKI (n = 968) | AKI (n = 151) | P Value |
|------------------------|------------------|---------------|---------|
| APACHE IV score        | 67 [58 - 72]     | 79 [67 - 99]  | <.001   |
| Acute physiology score | 55 [42 - 71]     | 67 [55 - 85]  | <.001   |
| mSOFA score            | 5 [3 - 7]        | 8 [6 - 9]     | <.001   |
| Non-renal mSOFA score  | 5 [3 - 7]        | 7 [5 - 8]     | <.001   |

#### Therapy during the first 24h

|                        | No AKI (n = 968) | AKI (n = 151) | P Value |
|------------------------|------------------|---------------|---------|
| Source of infection     | 562 (58.1)       | 75 (49.7)     | <.001   |
| Abdominal              | 134 (13.8)       | 38 (25.2)     | <.001   |
| Cardiovascular          | 70 (7.2)         | 12 (7.9)      | .001    |
| Urinary tract           | 43 (4.4)         | 8 (5.3)       | .001    |
| CNS                    | 56 (5.8)         | 6 (4.0)       | .007    |
| Skin or soft tissue     | 22 (2.3)         | 5 (3.3)       | .003    |
| Other                  | 68 (7.1)         | 12 (8.2)      | <.001   |

#### Other

|                        | No AKI (n = 968) | AKI (n = 151) | P Value |
|------------------------|------------------|---------------|---------|
| Source of infection     | 562 (58.1)       | 75 (49.7)     | <.001   |
| Abdominal              | 134 (13.8)       | 38 (25.2)     | <.001   |
| Cardiovascular          | 70 (7.2)         | 12 (7.9)      | .001    |
| Urinary tract           | 43 (4.4)         | 8 (5.3)       | .001    |
| CNS                    | 56 (5.8)         | 6 (4.0)       | .007    |
| Skin or soft tissue     | 22 (2.3)         | 5 (3.3)       | .003    |
| Other                  | 68 (7.1)         | 12 (8.2)      | <.001   |
### Renal function during the first 24 hours

|                     | (n = 968) | Transient AKI (n = 151) | Persistent AKI (n = 426) |
|---------------------|-----------|-------------------------|--------------------------|
| **Creatinine, µmol/L** | 79 [60 - 102] | 136 [94 - 170]* | 183 [136 - 251]* †< .001 |
| **Urea, mmol/L**     | 6.7 [4.6 - 9.9] | 10.8 [8.2 - 15.3]* | 13.5 [9.5 - 19.5]* †< .001 |
| **Bicarbonate (minimal), mmol/L** | 22.3 [19.1 - 25.9] | 19.3 [16.2 - 22.9]* | 16.1 [13.0 - 19.9]* †< .001 |
| **Urine output, mL** | 1900 [1303 - 2815] | 1380 [965 - 2354]* | 873 [391 - 1594]* †< .001 |

### Outcome

| **Outcome**                      |                      | Transient AKI (n = 151) | Persistent AKI (n = 426) |
|----------------------------------|----------------------|-------------------------|--------------------------|
| **Duration of initial MV, days** |                      | 2 [1 - 5]               | 3 [2 - 8]*               | 2 [1 - 7]†< .001 |
| **Reurrence of MV**              |                      | 24 [2.5]                | 11 [7.3]*               | 22 [5.2]* .002 |
| **MV-free days**                 |                      | 86 [46 - 89]            | 83 [31 - 88]            | 28 [1 - 85]* †< .001 |
| **Use of RRT**                   |                      | 25 [2.6]                | 9 [6.0]                 | 159 [37.3]* †< .001 |
| **RRT-free days**                |                      | 90 [59 - 90]            | 90 [43 - 90]*           | 38 [3 - 90]* †< .001 |

### Complications\(^a\)

| **Complications**                |                      | Transient AKI (n = 151) | Persistent AKI (n = 426) |
|----------------------------------|----------------------|-------------------------|--------------------------|
| None                             | 870 (89.9)           | 129 (85.4)              | 366 (85.9)              | .049 |
| ICU-acquired AKI                  | 57 (5.9)             | 6 (4.0)                 | 10 (2.3)*               | .011 |
| ICU-acquired ARDS                 | 20 (2.1)             | 5 (3.3)                 | 8 (1.9)                 | .57 |
| ICU-acquired infection            | 47 (4.9)             | 18 (11.9)*              | 48 (11.3)*              | < .001 |
| **ICU length of stay, days**     |                      | 4 [2 - 8]               | 7 [4 - 12]*             | 4 [2 - 11]†< .001 |
| **Hospital length of stay, days**|                      | 16 [8 - 29]            | 21 [12 - 38]*           | 14 [4 - 32]* †< .001 |
| **ICU-mortality**                |                      | 109 (11.3)             | 18 (11.9)               | 173 (40.6)* †< .001 |
| **30-day mortality**             |                      | 197 (20.4)             | 29 (19.2)               | 195 (45.8)* †< .001 |
| **60-day mortality**             |                      | 245 (25.3)             | 43 (28.5)               | 218 (51.2)* †< .001 |
| **90-day mortality**             |                      | 274 (28.3)             | 48 (31.8)               | 230 (54.0)* †< .001 |
| **1-year mortality**             |                      | 385 (37.7)             | 61 (40.4)               | 257 (60.3)* †< .001 |
| **ICU-free days**                |                      | 84 [45 - 87]           | 81 [28 - 86]*           | 32 [0 - 84]* †< .001 |

**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFa, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson \( \chi^2 \) test or the Fisher’s exact test when appropriate. \( P \) value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

\(^a\) Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

\(^b\) Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

\(^c\) Other sites of infection: Infections of bones and joints (n=19), Oral infections (n=8), Postoperative wound infections (n=20), Upper respiratory tract infections (n=20), Viral systemic infections (n=6), Endometritis (n=4), Other (n=27).

\(^d\) Between inclusion and day-90.

\(^e\) Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
| Demographics | No AKI (n = 968) | Transient AKI (n = 167) | Persistent AKI (n = 410) | P Value |
|--------------|-----------------|------------------------|--------------------------|---------|
| Age, years   | 62 [48 - 71]    | 64 [51 - 73]*          | 65 [54 - 73]†           | <.001   |
| Male sex     | 606 (62.6)      | 95 (56.9)              | 241 (58.8)              | .21     |
| Race, white  | 847 (88.0)      | 147 (88.0)             | 362 (89.8)              | .64     |
| Medical admission | 721 (74.5) | 122 (73.1)             | 294 (71.7)              | .56     |
| Chronic comorbidities |          |                       |                         |         |
| None         | 318 (32.9)      | 45 (26.9)              | 121 (29.5)              | .21     |
| Cardiovascular compromise | 229 (23.7) | 54 (32.3)              | 107 (26.1)              | .05     |
| Hypertension | 229 (23.7)      | 53 (31.7)              | 116 (28.3)              | .034    |
| Diabetes     | 159 (16.4)      | 37 (22.2)              | 75 (18.3)               | .17     |
| Liver cirrhosis | 13 (1.3) | 5 (3.0)                | 14 (3.4)                | .024    |
| Immune compromise | 184 (19.0) | 33 (19.8)              | 79 (19.3)               | .96     |
| Malignancy   | 200 (20.7)      | 37 (22.2)              | 97 (23.7)               | .44     |
| Charlson comorbidity index | 3 [1 - 5] | 3 [2 - 5]*             | 3 [2 - 5]*              | <.001   |
| Chronic medication |          |                       |                         |         |
| Diuretics    | 185 (19.1)      | 42 (25.1)              | 104 (25.4)*             | .016    |
| ACE inhibitors / ARBs | 223 (23.0) | 41 (24.6)              | 111 (27.1)              | .28     |
| Calcium-entry blockers | 122 (12.6) | 26 (15.6)              | 60 (14.6)               | .40     |
| Beta-adrenergic blockers | 222 (22.9) | 47 (28.1)              | 116 (28.3)              | .06     |
| NSAIDs and Cox II inhibitors | 112 (11.6) | 20 (12.0)              | 45 (11.0)               | .91     |
| Oral antidiabetic drugs | 113 (11.7) | 30 (18.0)              | 52 (12.7)               | .09     |
| Corticosteroids | 99 (10.2) | 17 (10.2)              | 39 (9.5)                | .94     |
| Antiplatelet drugs | 208 (22.5) | 40 (24.8)              | 96 (24.1)               | .71     |
| Severity at time of admission to ICU |          |                       |                         |         |
| APACHE IV score | 67 [52 - 85] | 81 [67 - 99]*          | 97 [75 - 121]**         | <.001   |
| Acute physiology score | 65 [42 - 71] | 68 [56 - 85]*          | 83 [63 - 107]**         | <.001   |
| mSOFA score | 5 [3 - 7]       | 8 [6 - 9]*             | 10 [7 - 12]**           | <.001   |
| Non-renal mSOFA score | 5 [3 - 7] | 7 [5 - 8]*             | 8 [6 - 9]**             | <.001   |
| Shock        | 362 (37.4)      | 117 (70.1)*            | 305 (74.4)**            | <.001   |
| ARDS         | 192 (19.8)      | 45 (26.9)              | 120 (29.3)**            | <.001   |
| Therapy during the first 24h |          |                       |                         |         |
| Mechanical ventilation | 773 (79.9) | 142 (85.0)             | 343 (83.7)              | .12     |
| Vasopressors | 503 (52.0)      | 135 (80.8)*            | 341 (83.2)**            | <.001   |
| Dose of vasopressors (mg)* | 5.8 [2.0 - 13.3] | 12.4 [5.0 - 22.4]* | 15.8 [5.7 - 34.6]** | <.001   |
| Inotropes    | 40 (4.1)        | 22 (13.2)**            | 70 (17.1)**             | <.001   |
| Dose of inotropes (mg)* | 151.3 [46.7 - 254.7] | 131.9 [63.8 - 275.0] | 193.1 [63.2 - 330.8] | .46     |
| RRT          | 6 (0.6)         | 7 (4.2)*               | 94 (23.0)**             | <.001   |
| Nephrototoxic drugs (≥ one) | 379 (39.2) | 85 (50.9)*             | 252 (61.5)*             | <.001   |
| Aminoglycoside | 128 (13.2) | 33 (19.8)              | 120 (29.3)*             | <.001   |
| Glycopeptide | 106 (11.0)      | 20 (12.0)              | 70 (17.1)*              | .09     |
| Colloid      | 163 (16.8)      | 47 (28.1)*             | 158 (38.5)*             | <.001   |
| Other*       | 94 (9.7)        | 16 (9.6)               | 31 (7.6)                | .44     |
| Source of infection |          |                       |                         |         |
| Pulmonary tract | 562 (58.1) | 81 (48.5)              | 137 (33.4)**            | <.001   |
| Abdominal    | 134 (13.8)      | 42 (25.1)*             | 114 (27.8)**            | <.001   |
| Cardiovascular | 70 (7.2) | 15 (9.0)               | 55 (13.4)*              | .002    |
| Urinary tract | 43 (4.4)       | 9 (5.4)                | 41 (10.0)*              | .001    |
| CNS          | 56 (5.8)        | 7 (4.2)                | 8 (2.0)*                | .004    |
| Skin or soft tissue | 22 (2.3) | 6 (3.6)                | 24 (5.9)*               | .004    |
| Other*       | 78 (8.1)        | 7 (4.2)                | 19 (4.6)                | .027    |
| Unknown      | 3 (0.3)         | 0 (0.0)                | 12 (2.9)*               | <.001   |
### Renal function during the first 24 hours

|                      | No AKI (n = 968) | Transient AKI (n = 167) | Persistent AKI (n = 410) | P Value |
|----------------------|------------------|-------------------------|-------------------------|---------|
| Creatinine, µmol/L   | 79 [60 - 102]    | 136 [95 - 171]*        | 186 [137 - 253]†        | <.001   |
| Urea, mmol/L         | 6.7 [4.6 - 9.9]  | 11.0 [8.2 - 15.3]*     | 13.5 [9.6 - 19.5]†      | <.001   |
| Bicarbonate (minimal), mmol/L | 22.3 [19.1 - 25.9] | 19.2 [16.3 - 22.9]* | 16.0 [13.0 - 19.7]†     | <.001   |
| Urine output, mL     | 1900 [1303 - 2815] | 1363 [956 - 2319]*   | 858 [368 - 1567]†       | <.001   |

**Outcome**

|                      | No AKI (n = 968) | Transient AKI (n = 167) | Persistent AKI (n = 410) | P Value |
|----------------------|------------------|-------------------------|-------------------------|---------|
| Duration of initial MV, days | 2 [1 - 5]       | 4 [2 - 8]*              | 2 [1 - 7]†              | <.001   |
| Recurrence of MV     | 24 (2.5)         | 13 (7.8)*               | 20 (4.9)                | .001    |
| MV-free days<sup>d</sup> | 86 [46 - 89]    | 82 [28 - 88]*           | 26 [1 - 85]†            | <.001   |
| Use of RRT           | 25 (2.6)         | 12 (7.2)*               | 156 (38.0)†             | <.001   |
| RRT-free days<sup>d</sup> | 90 [59 - 90]    | 90 [40 - 90]            | 37 [3 - 90]†            | <.001   |

**Complications<sup>a</sup>**

|                      | No AKI (n = 968) | Transient AKI (n = 167) | Persistent AKI (n = 410) | P Value |
|----------------------|------------------|-------------------------|-------------------------|---------|
| ICU-acquired AKI     | 57 (5.9)         | 6 (3.6)                 | 10 (2.4)*               | .016    |
| ICU-acquired ARDS    | 20 (2.1)         | 6 (3.6)                 | 7 (1.7)                 | .36     |
| ICU-acquired infection | 47 (4.9)      | 21 (12.6)*              | 45 (11.0)*              | <.001   |
| ICU length of stay, days | 4 [2 - 8]       | 7 [4 - 12]*             | 4 [2 - 11]†            | <.001   |
| Hospital length of stay, days | 16 [8 - 29] | 22 [12 - 38]*           | 14 [4 - 32]†            | <.001   |
| ICU-mortality        | 109 (11.3)       | 22 (13.2)               | 169 (41.2)†             | <.001   |
| 30-day mortality     | 197 (20.4)       | 35 (21.0)               | 189 (46.1)†             | <.001   |
| 60-day mortality     | 245 (25.3)       | 49 (29.3)               | 212 (51.7)†             | <.001   |
| 90-day mortality     | 274 (28.3)       | 54 (32.3)               | 224 (54.6)†             | <.001   |
| 1-year mortality     | 365 (37.7)       | 69 (41.3)               | 249 (60.7)†             | <.001   |
| ICU-free days<sup>d</sup> | 84 [45 - 87]    | 80 [24 - 85]*           | 28 [0 - 84]†            | <.001   |

**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson $\chi^2$ test or the Fisher’s exact test when appropriate. $P$ value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

<sup>a</sup> Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

<sup>b</sup> Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

<sup>c</sup> Other sites of infection: Infections of bones and joints (n=19), Oral infections (n=8), Postoperative wound infections (n=20), Upper respiratory tract infections (n=20), Viral systemic infections (n=6), Endometritis (n=4), Other (n=27).

<sup>d</sup> Between inclusion and day-90.

* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
Table 31. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis and with plasma biomarkers measured upon admission, stratified according to the presence and evolution of acute kidney injury based on a 72-hour cutoff

| Demographics                  | No AKI (n = 497) | Transient AKI | Persistent AKI (n = 272) | P Value |
|-------------------------------|------------------|---------------|--------------------------|---------|
| Age, years                    | 61 [48 - 70]     | 63 [53 - 73]* | 64 [54 - 72]*            | .001    |
| Male sex                      | 306 (61.6)       | 49 (50.5)     | 155 (57.0)               | .10     |
| Race, white                    | 426 (85.9)       | 84 (86.6)     | 236 (88.1)               | .72     |
| Medical admission             | 371 (74.6)       | 72 (74.2)     | 196 (72.1)               | .73     |
| Chronic comorbidities         |                  |               |                          |         |
| None                          | 159 (32.0)       | 25 (25.8)     | 81 (29.8)                | .47     |
| Cardiovascular compromise     | 114 (22.9)       | 27 (27.8)     | 71 (26.1)                | .43     |
| Hypertension                  | 111 (22.3)       | 35 (36.1)*    | 67 (24.6)                | .019    |
| Diabetes                      | 78 (15.7)        | 24 (24.7)     | 44 (16.2)                | .10     |
| Liver cirrhosis               | 10 (2.0)         | 2 (2.1)       | 10 (3.7)                 | .37     |
| Immune compromise             | 109 (21.9)       | 19 (19.6)     | 56 (20.6)                | .86     |
| Malignancy                    | 105 (21.1)       | 19 (19.6)     | 70 (25.7)                | .27     |
| Charlson comorbidity index    | 3 [1 - 5]        | 3 [2 - 5]     | 3 [2 - 5]*               | .027    |
| Chronic medication            |                  |               |                          |         |
| Diuretics                     | 90 (18.1)        | 25 (25.8)     | 71 (26.1)*               | .019    |
| ACE inhibitors / ARBs         | 101 (20.3)       | 25 (25.8)     | 72 (26.5)                | .11     |
| Calcium-entry blockers        | 58 (11.7)        | 20 (20.6)     | 35 (12.9)                | .06     |
| Beta-adrenergic blockers      | 105 (21.1)       | 26 (26.8)     | 67 (24.6)                | .32     |
| NSAIDs and Cox II inhibitors  | 61 (12.3)        | 15 (15.5)     | 36 (13.2)                | .65     |
| Oral antidiabetic drugs       | 50 (10.1)        | 20 (20.6)*    | 31 (11.4)                | .018    |
| Corticosteroids               | 62 (12.5)        | 10 (10.3)     | 26 (9.6)                 | .46     |
| Antiplatelet drugs            | 101 (21.7)       | 24 (25.3)     | 66 (25.1)                | .51     |
| Severity at time of admission to ICU | | | | |
| APACHE IV score               | 69 [54 - 88]     | 81 [65 - 101]*| 96 [77 - 119]*†          | <.001   |
| Acute physiology score        | 57 [44 - 71]     | 66 [55 - 80]* | 82 [56 - 107]*†          | <.001   |
| mSOFA score                   | 6 [4 - 8]        | 8 [6 - 9]*    | 10 [8 - 13]*†            | <.001   |
| Non-renal mSOFA score         | 6 [4 - 7]        | 7 [5 - 8]*    | 8 [7 - 10]*              | <.001   |
| Shock                         | 209 (42.1)       | 64 (66.0)*    | 211 (77.6)*              | <.001   |
| ARDS                          | 144 (29.0)       | 32 (33.0)     | 99 (36.4)                | .10     |
| Therapy during the first 24h  |                  |               |                          |         |
| Mechanical ventilation        | 427 (85.9)       | 82 (84.5)     | 229 (84.2)               | .77     |
| Vasopressors                  | 295 (59.4)       | 74 (76.3)*    | 237 (87.1)*†             | <.001   |
| Dose of vasopressors (mg)*    | 5.9 [2.2 - 13.9] | 12.8 [5.1 - 22.2]* | 16.0 [5.6 - 37.5]*†     | <.001   |
| Inotropes                     | 16 (3.2)         | 10 (10.3)*    | 43 (15.8)*               | <.001   |
| Dose of inotropes (mg)*       | 159.2 [44.4 - 281.5] | 148.9 [126.3 - 304.0] | 222.3 [73.0 - 325.5]     | .64     |
| RRT                           | 4 (0.8)          | 6 (6.2)*      | 71 (26.2)*†              | <.001   |
| Nephrotoxic drugs (≥ one)     | 223 (44.9)       | 47 (48.5)     | 190 (69.9)*†             | <.001   |
| Aminoglycoside                | 86 (17.3)        | 21 (21.6)     | 86 (31.6)*               | <.001   |
| Glycopeptide                  | 60 (12.1)        | 9 (9.3)       | 55 (20.2)*               | .004    |
| Colloid                       | 110 (22.1)       | 29 (29.9)     | 122 (44.9)*†             | <.001   |
| Other*                        | 42 (8.5)         | 7 (7.2)       | 25 (9.2)                 | .86     |
| Source of infection           |                  |               |                          |         |
| Pulmonary tract               | 298 (60.0)       | 44 (45.4)*    | 96 (35.3)*               | <.001   |
| Abdominal                     | 77 (15.5)        | 29 (29.9)*    | 72 (26.5)*               | <.001   |
| Cardiovascular                | 48 (9.7)         | 9 (9.3)       | 38 (14.0)                | .18     |
| Urinary tract                 | 20 (4.0)         | 6 (6.2)       | 26 (9.6)                 | .010    |
| CNS                           | 22 (4.4)         | 2 (2.1)       | 5 (1.8)                  | .15     |
| Skin or soft tissue           | 13 (2.6)         | 4 (4.1)       | 21 (7.7)*                | .004    |
| Other*                        | 19 (3.8)         | 3 (3.1)       | 8 (2.9)                  | .89     |
| Unknown                       | 0 (0.0)          | 0 (0.0)       | 6 (2.2)*                 | .004    |
### Renal function during the first 24 hours

|                          | No AKI (n = 497) | Transient AKI (n = 97) | Persistent AKI (n = 272) | P Value |
|--------------------------|------------------|------------------------|--------------------------|---------|
| Creatinine, µmol/L       | 79 [61 - 105]    | 133 [94 - 170]*        | 180 [132 - 251]*†        | <.001   |
| Urea, mmol/L             | 6.9 [4.7 - 10.1] | 10.6 [8.0 - 15.1]*     | 13.5 [9.3 - 19.3]*        | <.001   |
| Bicarbonate (minimal), mmol/L | 22.1 [18.9 - 25.8] | 18.8 [16.1 - 22.5]*     | 16.1 [13.3 - 19.3]*†      | <.001   |
| Urine output, mL         | 1820 [1315 - 2750] | 1288 [943 - 2091]*          | 930 [435 - 1546]*†         | <.001   |

### Outcome

|                          | No AKI (n = 497) | Transient AKI (n = 97) | Persistent AKI (n = 272) | P Value |
|--------------------------|------------------|------------------------|--------------------------|---------|
| Duration of initial MV, days | 2 [1 - 7]         | 4 [2 - 8]              | 3 [1 - 8]                | .12     |
| Recurrence of MV         | 13 (2.6)          | 7 (7.2)                | 14 (5.1)                 | .040    |
| MV-free days             | 84 [29 - 88]      | 83 [36 - 88]           | 30 [1 - 85]*†            | <.001   |
| Use of RRT               | 18 (3.6)          | 7 (7.2)                | 115 (42.3)*†             | <.001   |
| RRT-free days            | 90 [44 - 90]      | 90 [51 - 90]           | 40 [3 - 90]*†            | <.001   |

### Complications

|                          | No AKI (n = 497) | Transient AKI (n = 97) | Persistent AKI (n = 272) | P Value |
|--------------------------|------------------|------------------------|--------------------------|---------|
| None                     | 430 (86.5)       | 82 (84.5)              | 229 (84.2)               | .64     |
| ICU-acquired AKI         | 41 (8.2)         | 4 (4.1)                | 10 (3.7)*                | .031    |
| ICU-acquired ARDS        | 15 (3.0)         | 3 (3.1)                | 6 (2.2)                  | .79     |
| ICU-acquired infection   | 32 (6.4)         | 13 (13.4)              | 33 (12.1)*               | .007    |
| ICU length of stay, days | 5 [3 - 9]        | 7 [4 - 12]*            | 5 [3 - 12]*†             | <.001   |
| Hospital length of stay, days | 17 [10 - 33]   | 25 [13 - 42]*          | 16 [6 - 35]*†            | <.001   |
| ICU-mortality            | 64 (12.9)        | 10 (10.3)              | 109 (40.1)*†             | <.001   |
| 30-day mortality         | 107 (21.5)       | 16 (16.5)              | 120 (44.1)*†             | <.001   |
| 60-day mortality         | 139 (28.0)       | 26 (26.8)              | 136 (50.7)*†             | <.001   |
| 90-day mortality         | 157 (31.6)       | 29 (29.9)              | 147 (54.0)*†             | <.001   |
| 1-year mortality         | 202 (40.6)       | 39 (40.2)              | 167 (61.4)*†             | <.001   |
| ICU-free days            | 82 [33 - 86]     | 80 [45 - 85]           | 34 [0 - 83]*†            | <.001   |

**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

* Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

Other sites of infection: Infections of bones and joints (n=8), Oral infections (n=3), Postoperative wound infections (n=4), Upper respiratory tract infections (n=7), Viral systemic infections (n=4), Other (n=4)

Between inclusion and day-90.

*Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### Table 32. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis and with plasma biomarkers measured upon admission, stratified according to the presence and evolution of acute kidney injury based on a 96-hour cutoff

| Demographics          | No AKI (n = 497) | Transient AKI (n = 111) | Persistent AKI (n = 258) | P Value |
|-----------------------|------------------|------------------------|--------------------------|---------|
| **Age, years**        | 61 [48 - 70]     | 63 [53 - 73]*          | 64 [54 - 72]*            | .001    |
| **Male sex**          | 306 (61.6)       | 56 (50.5)              | 148 (57.4)               | .08     |
| **Race, white**       | 426 (85.9)       | 96 (86.5)              | 224 (88.2)               | .69     |
| **Medical admission** | 371 (74.6)       | 81 (73.0)              | 187 (72.5)               | .80     |
| **Chronic comorbidities** |                 |                        |                          |         |
| None                  | 159 (32.0)       | 29 (26.1)              | 77 (29.8)                | .47     |
| Cardiovascular        | 114 (22.9)       | 30 (27.0)              | 68 (26.4)                | .45     |
| Hypertension          | 111 (22.3)       | 39 (35.1)*             | 63 (24.4)                | .021    |
| Diabetes              | 78 (15.7)        | 26 (23.4)              | 42 (16.3)                | .15     |
| Liver cirrhosis       | 10 (2.0)         | 2 (2.7)                | 9 (3.5)                  | .45     |
| Immune compromise     | 109 (21.9)       | 23 (20.7)              | 52 (20.2)                | .86     |
| Malignancy            | 105 (21.1)       | 24 (21.6)              | 65 (25.2)                | .43     |
| Charlson comorbidity index | 3 [1 - 5]       | 3 [2 - 5]*             | 3 [2 - 5]*               | .027    |
| **Chronic medication**|                 |                        |                          |         |
| Diuretics             | 90 (18.1)        | 28 (25.2)              | 68 (26.4)*               | .18     |
| ACE inhibitors / ARBs | 101 (20.3)       | 28 (25.2)              | 69 (26.7)                | .11     |
| Calcium-entry blockers| 58 (11.7)        | 20 (18.0)              | 35 (13.6)                | .19     |
| Beta-adrenergic blockers| 105 (21.1)    | 30 (27.0)              | 63 (24.4)                | .31     |
| NSAIDs and Cox II inhibitors | 61 (12.3)   | 18 (16.2)              | 33 (12.8)                | .51     |
| Oral antidiabetic drugs| 50 (10.1)        | 21 (18.9)*             | 30 (11.6)                | .038    |
| Corticosteroids       | 62 (12.5)        | 12 (10.8)              | 24 (9.3)                 | .43     |
| Antiplatelet drugs    | 101 (21.7)       | 25 (23.4)              | 65 (25.9)                | .45     |
| **Severity at time of admission to ICU** |                  |                        |                          |         |
| APACHE IV score       | 69 [54 - 88]     | 81 [68 - 101]*         | 97 [77 - 120]**          | <.001   |
| Acute physiology score| 57 [44 - 71]     | 68 [56 - 82]*          | 83 [64 - 107]**†         | <.001   |
| mSOFA score           | 6 [4 - 8]        | 8 [6 - 9]*             | 10 [8 - 13]*†            | <.001   |
| Non-renal mSOFA score | 6 [4 - 7]        | 7 [5 - 8]*             | 8 [7 - 10]*†             | <.001   |
| Shock                 | 209 (42.1)       | 76 (68.5)*             | 199 (77.1)*              | <.001   |
| ARDS                  | 144 (29.0)       | 37 (33.3)              | 94 (36.4)                | .10     |
| **Therapy during the first 24h** |                     |                        |                          |         |
| Mechanical ventilation| 427 (85.9)       | 93 (83.8)              | 218 (84.5)               | .76     |
| Vasopressors          | 295 (59.4)       | 87 (78.4)*             | 224 (86.6)*              | <.001   |
| Dose of vasopressors (mg)* | 5.9 [2.2 - 13.9] | 13.5 [5.1 - 23.7]*    | 15.9 [5.6 - 37.9]*       | <.001   |
| Inotropes             | 16 (3.2)         | 13 (11.7)*             | 40 (15.5)*               | <.001   |
| Dose of inotropes (mg)* | 159.2 [44.4 - 281.5] | 147.3 [110.0 - 291.4] | 223.9 [77.3 - 341.2]    | .59     |
| RRT                   | 4 (0.8)          | 7 (6.3)*               | 70 (27.2)*†              | <.001   |
| Nephrotoxic drugs (≥ one) | 223 (44.9)   | 57 (51.4)              | 180 (69.8)*†             | <.001   |
| Aminoglycoside        | 86 (17.3)        | 24 (21.6)              | 83 (32.2)*               | <.001   |
| Glycopeptide          | 60 (12.1)        | 11 (9.9)               | 53 (20.5)*†              | .003    |
| Colloid               | 110 (22.1)       | 37 (33.3)              | 114 (44.2)*              | <.001   |
| Other a               | 42 (8.5)         | 8 (7.2)                | 24 (9.3)                 | .83     |
| **Source of infection** |                 |                        |                          |         |
| Pulmonary tract       | 298 (60.0)       | 48 (43.2)*             | 92 (35.7)*               | <.001   |
| Abdominal             | 77 (15.5)        | 33 (29.7)*             | 68 (26.4)*               | <.001   |
| Cardiovascular        | 48 (9.7)         | 12 (10.8)              | 35 (13.6)                | .26     |
| Urinary tract         | 20 (4.0)         | 7 (6.3)                | 25 (9.7)                 | .008    |
| CNS                   | 22 (4.4)         | 3 (2.7)                | 4 (1.6)                  | .11     |
| Skin or soft tissue   | 13 (2.6)         | 5 (4.5)                | 20 (7.8)*                | .005    |
| Other c               | 19 (3.8)         | 3 (2.7)                | 8 (3.1)                  | .86     |
| Unknown               | 0 (0.0)          | 0 (0.0)                | 6 (2.3)*                 | .001    |
eTable 32 continued

| Renal function during the first 24 hours | No AKI (n = 497) | Transient AKI (n = 111) | Persistent AKI (n = 258) | P Value  |
|----------------------------------------|-----------------|------------------------|-------------------------|----------|
| Creatinine, µmol/L                     | 79 [61 - 105]   | 134 [95 - 174]*        | 185 [134 - 253]†        | <.001    |
| Urea, mmol/L                           | 6.9 [4.7 - 10.1]| 10.7 [8.3 - 15.1]*     | 13.7 [9.4 - 19.5]*      | <.001    |
| Bicarbonate (minimal), mmol/L          | 22.1 [18.9 - 25.8]| 18.8 [16.3 - 22.8]*     | 16.0 [13.1 - 19.0]†     | <.001    |
| Urine output, mL                       | 1820 [1315 - 2750]| 1275 [919 - 2069]*     | 915 [420 - 1504]*†      | <.001    |

Outcome

| Duration of initial MV, days           | 2 [1 - 7]       | 4 [2 - 8.50]           | 3 [1 - 8]               | .11      |
| Recurrence of MV                      | 13 (2.6)        | 8 (7.2)                | 13 (5.0)                | .040     |
| MV-free days                         | 84 [29 - 88]    | 81 [32 - 88]           | 27 [1 - 85]†            | <.001    |
| Use of RRT                            | 18 (3.6)        | 10 (9.0)               | 112 (43.4)†             | <.001    |
| RRT-free days                         | 90 [44 - 90]    | 90 [43 - 90]           | 37 [3 - 90]†            | <.001    |

Complications*

| None                                   | 430 (86.5)      | 93 (83.8)              | 218 (84.5)              | .61      |
| ICU-acquired AKI                       | 41 (8.2)        | 4 (3.6)                | 10 (3.9)                | .032     |
| ICU-acquired ARDS                      | 15 (3.0)        | 4 (3.6)                | 5 (1.9)                 | .38      |
| ICU-acquired infection                 | 32 (6.4)        | 16 (14.4)              | 30 (11.6)               | .006     |
| ICU length of stay, days               | 5 [3 - 9]       | 8 [5 - 12]*            | 5 [3 - 12]†             | <.001    |
| Hospital length of stay, days         | 17 [10 - 33]    | 24 [13 - 43]*          | 15 [5 - 34]†            | <.001    |
| ICU-mortality                          | 64 (12.9)       | 14 (12.6)              | 105 (40.7)†             | <.001    |
| 30-day mortality                      | 107 (21.5)      | 22 (19.8)              | 114 (44.2)†             | <.001    |
| 60-day mortality                      | 139 (28.0)      | 32 (28.8)              | 132 (51.2)†             | <.001    |
| 90-day mortality                      | 157 (31.6)      | 35 (31.5)              | 141 (54.7)†             | <.001    |
| 1-year mortality                      | 202 (40.6)      | 47 (42.3)              | 159 (61.6)†             | <.001    |
| ICU-free days                         | 82 [33 - 86]    | 79 [36 - 85]           | 32 [0 - 83]†            | <.001    |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson χ² test or the Fisher’s exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

[Additional notes and footnotes as per the original document]
### eTable 33. Host response biomarkers in patients with sepsis during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission based on a 72-hour cutoff

|                     | Admission                | Day-2                    | Day 4                    | P Value (group) | P Value (time x group) |
|---------------------|--------------------------|--------------------------|--------------------------|-----------------|------------------------|
|                     | No AKI (n= 497)          | Transient AKI (n= 272)   | Persistent AKI (n= 95)   | No AKI (n= 242) | Transient AKI (n= 63)   | Persistent AKI (n= 137) |                  |                  |
| **Inflammatory responses** |                          |                          |                          |                 |                        |                      |                  |                  |
| IL-10 (pg/mL)       | 7.2                      | 18.8                     | 45.3                     | 4.3             | 7.5                    | 18.1                  | 3.5              | 4.6              | 14.2              | <0.001              | <0.001                |
|                     | [3.0-21.1]               | [8.4-53.1]*              | [12.5-193.6]*†           | [2.0-10.0]      | [3.4-16.5]*†           | [7.7-65.4]*††         | [1.8-8.0]         | [2.5-10.1]       | [5.3-36.2]*††     | <0.001              | <0.001                |
| IL-6 (pg/mL)        | 102.0                    | 331.0                    | 511.9                    | 44.2            | 66.7                   | 133.4                 | 27.0             | 31.5             | 62.6              | <0.001              | <0.001                |
|                     | [27.1-474.5]             | [74.4-1464.3]*           | [91.7-4555.5]*           | [15.1-149.5]    | [28.6-190.4]*          | [35.6-853.3]*††       | [10.7-108.1]      | [11.2-71.5]      | [20.1-139.8]*     | <0.001              | <0.001                |
| IL-8 (pg/mL)        | 61.5                     | 169.7                    | 363.1                    | 32.6            | 96.2                   | 173.0                 | 29.2             | 59.2             | 101.1             | <0.001              | <0.001                |
|                     | [24.2-182.7]             | [78.7-570.6]*            | [102.5-2080.6]*†         | [15.9-87.9]     | [36.3-179.3]*          | [69.0-696.6]*††       | [13.8-86.1]       | [31.6-130.6]*     | [61.2-277.6]*†     | <0.001              | <0.001                |
| MMP-8 (ng/mL)       | 2.6                      | 7.0                      | 6.1                      | 1.5             | 3.0                    | 4.0                   | 1.0              | 1.6              | 2.8               | <0.001              | 0.18                   |
|                     | [0.6-5.8]                | [2.0-16.9]*              | [1.8-15.9]*              | [0.5-3.9]       | [1.2-9.4]*             | [1.2-14.3]*           | [0.4-2.1]        | [0.7-3.7]*        | [0.8-7.8]*         | <0.001              |                      |
| **Endothelial cell activation** |                      |                          |                          |                 |                        |                      |                  |                  |                  |                    |                      |
| Fractalkine (pg/mL) | 19.9                     | 30.2                     | 49.4                     | 16.7            | 27.2                   | 51.4                  | 18.4             | 27.3             | 63.2              | <0.001              | 0.005                 |
|                     | [12.8-38.8]              | [15.0-64.2]*             | [22.8-109.3]*†           | [12.8-34.1]     | [13.4-66.4]*†          | [23.5-125.4]*††       | [12.8-44.9]      | [15.9-53.3]      | [33.6-141.1]*††   | <0.001              | 0.001                 |
| sE-Selectin (ng/mL) | 8.8                      | 12.1                     | 13.1                     | 8.9             | 11.1                   | 11.4                  | 7.6              | 9.7              | 8.7               | 0.001               | 0.015                 |
|                     | [4.2-21.2]               | [5.4-33.1]*              | [5.5-30.2]*              | [4.0-17.3]      | [4.7-24.6]             | [4.1-22.4]            | [3.6-15.1]       | [4.2-17.3]       | [4.5-18.0]        |                      |                      |
| sICAM-1 (ng/mL)     | 155.7                    | 185.2                    | 223.6                    | 169.4           | 195.1                  | 269.2                 | 203.6            | 219.5            | 271.1             | <0.001              | 0.77                  |
|                     | [88.2-286.5]             | [105.6-133.0]            | [133.0-388.2]*           | [105.3-300.3]   | [121.6-330.8]          | [138.7-435.6]*‡       | [109.8-335.5]    | [129.4-353.6]    | [177.9-419.1]*††  | <0.001              | <0.001                |
| Angiopoietin-1 (ng/mL) | 2.6                      | 3.1                      | 1.7                      | 2.0             | 2.0                    | 1.7                   | 2.1              | 2.0             | 0.8               | <0.001              | 0.005                 |
|                     | [1.0-6.2]                | [1.1-7.8]                | [0.7-3.4]*††             | [0.9-5.3]       | [0.9-3.2]              | [0.6-1.9]*††          | [0.9-4.7]        | [0.7-4.0]        | [0.4-2.1]*††      | <0.001              | <0.001                |
| Angiopoietin-2 (ng/mL) | 4.7                      | 8.8                      | 12.0                     | 5.5             | 8.6                    | 16.8                  | 4.0              | 5.6             | 9.5               | <0.001              | <0.001                |
|                     | [2.2-9.3]                | [3.9-19.6]*              | [5.5-26.0]*              | [2.6-10.3]      | [4.0-19.9]*            | [9.3-43.2]*††         | [2.0-9.4]        | [3.7-10.8]       | [4.7-23.1]*††     | <0.001              | 0.22                  |
| ANG-2:ANG-1 (ng/mL) | 1.7                      | 2.4                      | 8.2                      | 2.3             | 5.0                    | 20.0                  | 1.7              | 3.6             | 14.6              | <0.001              | 0.99                  |
|                     | [0.5-6.1]                | [0.7-13.1]               | [2.3-26.2]*              | [0.6-9.2]       | [1.7-17.3]*            | [6.9-55.1]*††         | [0.5-7.6]        | [1.1-9.4]        | [4.6-36.6]*††     | <0.001              |                      |
### eTable 33 continued

|                  | Admission                        | Day-2                        | Day 4                        | P Value (group) | P Value (time x group) |
|------------------|----------------------------------|------------------------------|------------------------------|-----------------|------------------------|
|                  | No AKI (n= 497)                  | Transient AKI (n= 97)        | Persistent AKI (n= 272)      | No AKI (n= 374) | Transient AKI (n= 95) | Persistent AKI (n= 195) | No AKI (n= 242) | Transient AKI (n= 63) | Persistent AKI (n= 137) |                  |
| **Coagulation activation** |                                  |                              |                              |                 |                        |                           |                 |                        |                          |                  |
| D-dimer (µg/mL)  | 7.3 [3.3-15.4]                   | 8.7 [3.2-16.1]†             | 12.0 [5.9-22.5]‡             | 6.3 [3.3-12.7]  | 9.7 [4.5-15.3]†        | 14.0 [6.4-24.1]‡          | 8.3 [4.5-16.0] | 8.5 [4.9-18.4]        | 12.7 [6.9-22.9]‡        | <0.001 0.94  |
| Protein C (ng/mL)| 122.7 [90.0-159.0]†             | 103.6 [78.5-151.0]          | 111.2 [87.1-143.8]*          | 125.3           | 103.4                  | 114.7                      | 141.3 [100.8] | 130.7 [84.6-107.0]    | 150.6 [76.4-137.0]    | <0.001 0.033 |
| Antithrombin     | 773.7 [539.5-1111.2]             | 659.8 [423.5-981.6]         | 641.1 [402.0-964.1]*         | 778.7           | 601.8                  | 603.3                      | 934.4           | 779.7                  | 718.2               | <0.001 0.09  |
| PT (sec)         | 14.8 [12.5-17.3]†                | 15.3 [12.9-18.7]            | 16.8 [13.8-22.2]‡             | 14.0            | 14.0                   | 15.0                       | 14.0            | 14.0                   | 14.0                | <0.001 <0.001 |
| aPTT (sec)       | 34.0 [29.0-44.0]†                | 38.0 [32.0-48.8]            | 44.0 [35.0-62.5]‡             | 33.0            | 36.0                   | 44.0                       | 36.0            | 36.0                   | 39.0                | <0.001 0.09  |
| Platelets (10⁵/L)| 181.5 [123.0-261.2]             | 193.0 [113.0-254.0]         | 115.5 [46.0-197.5]‡           | 182.0           | 167.0                  | 111.0                      | 196.0           | 156.0                  | 73.5                | <0.001 0.001 |

Abbreviations: ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Data presented as median [interquartile range]

Overall P values are derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn’s post hoc tests of multiple comparisons using rank sums.

* Significant vs no AKI
† Significant vs Transient AKI

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**eTable 34. Host response biomarkers in patients with sepsis during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission based on a 96-hour cutoff**

|               | Inflammatory responses | Endothelial cell activation |
|---------------|------------------------|-----------------------------|
|               | Adm | Day-2 | Day 4 | P Value (group) | P Value (time x group) |
|               | AKI |       | AKI   |               |                           |
| IL-10 (pg/mL)|     |       |       |               |                           |
| No AKI (n=497)| 7.2 | 4.3   | 3.5    | <0.001       | <0.001                    |
| Transient AKI (n=374)| 20.4 | [2.0-10.0] | [1.8-8.0] |               |                           |
| Persistent AKI (n=258) | 45.8 | [3.6-18.7] | [2.8-10.6] |               |                           |
| IL-6 (pg/mL) |     |       |       |               |                           |
| No AKI (n=497) | 102.0 | 44.2 | 27.0 | <0.001       | <0.001                    |
| Transient AKI (n=374)| 337.3 | 69.8 | 32.7 |               |                           |
| Persistent AKI (n=258) | 511.9 | [15.1-149.5] | [12.4-74.8] |               |                           |
| IL-8 (pg/mL)|     |       |       |               |                           |
| No AKI (n=497) | 61.5 | 32.6 | 29.2 | <0.001       | <0.001                    |
| Transient AKI (n=374)| 175.5 | 105.8 | 59.2 |               |                           |
| Persistent AKI (n=258) | 372.2 | [15.9-87.9] | [13.8-86.1] |               |                           |
| MMP-8 (ng/mL)|     |       |       |               |                           |
| No AKI (n=497) | 2.6 | 1.5 | 1.0 | <0.001       | 0.38                      |
| Transient AKI (n=374)| 6.4 | 3.0 | 1.7 |               |                           |
| Persistent AKI (n=258) | 6.2 | [0.5-3.9] | [1.0-7.3] |               |                           |
| Fractalkine (pg/mL)| |     |       |               |                           |
| No AKI (n=497) | 19.9 | 16.7 | 18.4 | <0.001       |                           |
| Transient AKI (n=374)| 35.2 | 29.9 | 33.1 |               |                           |
| Persistent AKI (n=258) | 49.2 | [12.8-34.1] | [12.8-44.9] |               |                           |
| sE-Selectin (ng/mL)| |     |       |               |                           |
| No AKI (n=497) | 8.8 | 8.9 | 7.6 | <0.001       | 0.003                     |
| Transient AKI (n=374)| 12.0 | 11.1 | 8.9 |               |                           |
| Persistent AKI (n=258) | 13.1 | [4.0-10.7] | [4.6-16.0] |               |                           |
| sICAM-1 (ng/mL)| |     |       |               |                           |
| No AKI (n=497) | 155.7 | 169.4 | 203.6 | <0.001       |                           |
| Transient AKI (n=374)| 190.5 | 183.7 | 204.1 |               |                           |
| Persistent AKI (n=258) | 229.1 | [105.3-133.4] | [123.4-191.1] |               |                           |
| Angiopoietin-1 (ng/mL)| |     |       |               |                           |
| No AKI (n=497) | 2.6 | 2.0 | 2.1 | <0.001       | 0.016                     |
| Transient AKI (n=374)| 8.8 | 1.9 | 1.6 |               |                           |
| Persistent AKI (n=258) | 12.1 | [0.7-3.6] | [0.4-2.1] |               |                           |
| Angiopoietin-2 (ng/mL)| |     |       |               |                           |
| No AKI (n=497) | 4.7 | 5.5 | 4.0 | <0.001       | 0.22                      |
| Transient AKI (n=374)| 8.8 | 10.0 | 6.4 |               |                           |
| Persistent AKI (n=258) | 12.1 | [4.4-21.9] | [4.4-23.1] |               |                           |
| ANG-2:ANG-1 (ng/mL) | | | | <0.001 | 0.99 |
**eTable 34 continued**

|                      | No AKI (n=497) | Transient AKI (n=111) | Persistent AKI (n=258) | No AKI (n=374) | Transient AKI (n=109) | Persistent AKI (n=181) | No AKI (n=242) | Transient AKI (n=75) | Persistent AKI (n=125) | P Value (group) | P Value (time x group) |
|----------------------|----------------|----------------------|------------------------|----------------|----------------------|------------------------|----------------|---------------------|------------------------|----------------|----------------------|
| **Coagulation activation** |                |                      |                        |                |                      |                        |                |                     |                        |                |                      |
| D-dimer (µg/mL)      | 7.3            | 8.9                  | 11.9                   | 6.3            | 10.6                 | 13.7                   | 8.3            | 9.4                 | 13.1                   | <0.001         | 0.93                |
| [3.3-15.4]           | [3.9-19.0]     | [6.0-22.4]*†         | [3.3-12.7]            | [4.6-17.9]*†   | [6.3-24.6]*†         |                       | [4.5-16.0]     | [4.9-18.8]         | [6.9-22.9]*†         |                |                     |
| Protein C (ng/mL)    | 122.7          | 103.6                | 111.3                  | 125.3          | 103.0                | 115.4                  | 141.3          | 100.8               | 128.8 [83.2 - 108.2] | <0.001         | 0.052               |
| [90.0-159.0]         | [78.1-150.8]*† | [88.0-143.8]         | [94.8-169.1]          | [73.9-139.8]*† | [87.6-144.1]*†       |                       | 141.3          | 100.8               | 128.8 [83.2 - 108.2] |                |                     |
| Antithrombin (ng/mL) | 773.7          | 646.5                | 641.1                  | 778.7          | 601.1                | 607.4                  | 934.4          | 762.6               | 743.9                   | 0.001          | 0.24                |
| [539.5-1111.2]       | [411.5-996.5]* | [401.7-953.6]*       | [490.9-1130.6]       | [387.2-941.0]* | [418.8-914.6]*       |                       | 585.7          | 503.2               | 469.4 [1216.5-1195.3]*| 0.001         | 0.24                |
| PT (sec)             | 14.8           | 15.6                 | 17.0                   | 14.0           | 14.0                 | 15.0                   | 14.0           | 14.0                | 14.0                   | <0.001         | <0.001              |
| [12.5-17.3]          | [12.9-18.7]*†  | [13.8-22.4]*†        | [12.0-16.0]           | [13.0-18.0]    | [13.0-19.5]*†        | [12.0-15.0]           | [12.0-15.0]    | [12.0-15.8]         | [12.0-17.0]           | 0.001          |                     |
| aPTT (sec)           | 34.0           | 37.5                 | 45.0                   | 33.0           | 36.5                 | 45.0                   | 30.0           | 32.0                | 39.0                   | <0.001         | 0.06                |
| [29.0-44.0]          | [32.0-47.2]*†  | [35.0-64.0]*†        | [29.0-43.0]           | [31.8-43.0]    | [35.0-55.0]*†        | [26.0-45.8]           | [28.5-45.0]    | [33.0-48.8]*        |                        |                |                     |
| Platelets (10^9/L)   | 181.5          | 169.0                | 116.0                  | 182.0          | 160.0                | 111.0                  | 196.0          | 150.0               | 72.0                   | <0.001         | <0.001              |
| [123.0-261.2]        | [106.0-252.5]  | [198.5]*†            | [265.0]              | [116.5-274.5]  | [177.8]*†            | [274.5]              | [30.0-163.0]   |                     |                        |                |                     |

Abbreviations: ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-selectin, soluble E-selectin; sICAM-1, soluble intercellular adhesion molecule-1.

Data presented as median [interquartile range]

Overall P values are derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects.

Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn’s post hoc tests of multiple comparisons using rank sums.

* Significant vs no AKI
† Significant vs Transient AKI
eTable 35. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis and with blood genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury based on a 72-hour cutoff

| Demographics | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|--------------|------------------|------------------------|--------------------------|---------|
| Age, years   | 63 [49 - 70]     | 69 [53 - 75]           | 64 [56 - 72]             | .17     |
| Male sex     | 130 (57.8)       | 21 (46.7)              | 71 (58.2)                | .37     |
| Race, white  | 184 (82.5)       | 40 (88.9)              | 103 (86.6)               | .48     |
| Medical admission | 166 (73.8) | 33 (73.3)              | 82 (67.2)                | .43     |

| Chronic comorbidities | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|-----------------------|------------------|------------------------|--------------------------|---------|
| None                  | 74 (32.9)        | 14 (31.1)              | 43 (35.2)                | .86     |
| Cardiovascular compromise | 47 (20.9)       | 9 (20.0)               | 29 (23.8)                | .78     |
| Hypertension          | 50 (22.2)        | 18 (40.0)              | 31 (25.4)                | .049    |
| Diabetes              | 37 (16.4)        | 10 (22.2)              | 25 (20.5)                | .48     |

| Chronic medication | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|--------------------|------------------|------------------------|--------------------------|---------|
| Diuretics          | 44 (19.6)        | 14 (31.1)              | 34 (27.9)                | .09     |
| ACE inhibitors / ARBs | 46 (20.4)       | 11 (24.4)              | 36 (29.5)                | .16     |
| Calcium-entry blockers | 29 (12.9)       | 9 (20.0)               | 17 (13.9)                | .44     |
| Beta-adrenergic blockers | 52 (23.1)     | 15 (33.3)              | 39 (32.0)                | .11     |

| Severity at time of admission to ICU | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|-------------------------------------|------------------|------------------------|--------------------------|---------|
| APACHE IV score                     | 71 [57 - 89]     | 84 [73 - 101]*         | 91 [76 - 116]*           | <.001   |
| Acute physiology score              | 59 [47 - 72]     | 70 [59 - 84]*          | 80 [63 - 104]*           | <.001   |
| mSOFA score                         | 6 [4 - 8]        | 8 [6 - 9]*             | 10 [8 - 13]*             | <.001   |
| Non-renal mSOFA score               | 6 [4 - 7]        | 7 [6 - 9]*             | 8 [7 - 10]*              | <.001   |

| Therapy during the first 24h | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|-----------------------------|------------------|------------------------|--------------------------|---------|
| Mechanical ventilation      | 194 (86.2)       | 38 (84.4)              | 107 (87.7)               | .81     |
| Vasopressors                | 130 (57.8)       | 36 (80.0)*             | 111 (91.0)*              | <.001   |
| Dose of vasopressors (mg)*  | 5.9 [2.3 - 14.4] | 16.2 [4.6 - 33.2]*     | 18.6 [8.8 - 38.6]*       | <.001   |
| INtropes                    | 9 (4.0)          | 6 (13.3)*              | 25 (20.5)*               | <.001   |

| Source of infection | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|---------------------|------------------|------------------------|--------------------------|---------|
| Pulmonary tract      | 130 (57.8)       | 20 (44.4)              | 45 (36.9)*               | .001    |
| Abdominal            | 42 (18.7)        | 15 (33.3)              | 39 (32.0)*               | .007    |
| Cardiovascular       | 23 (10.2)        | 3 (6.7)                | 16 (13.1)                | .50     |
| Urinary tract        | 12 (5.3)         | 3 (6.7)                | 11 (9.0)                 | .41     |

| Source of infection | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|---------------------|------------------|------------------------|--------------------------|---------|
| CNS                 | 8 (3.6)          | 0 (0.0)                | 1 (0.8)                  | .23     |
| Skin or soft tissue | 8 (3.6)          | 2 (4.4)                | 9 (7.4)                  | .26     |
| Other*              | 2 (0.9)          | 2 (4.4)                | 0 (0.0)                  | .06     |

| Unknown              | 0 (0.0)          | 0 (0.0)                | 1 (0.8)                  | .43     |
## Renal function during the first 24 hours

|                          | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|--------------------------|------------------|------------------------|--------------------------|---------|
| Creatinine, µmol/L       | 80 [61 - 105]    | 134 [110 - 170]*       | 176 [140 - 244]†         | <.001   |
| Urea, mmol/L             | 7.1 [5.1 - 9.9]  | 10.5 [7.8 - 17.5]*     | 13.3 [9.4 - 18.1]*       | <.001   |
| Bicarbonate (minimal), mmol/L | 21.7 [18.2 - 26.2] | 18.8 [15.7 - 22.5]* | 16.2 [13.4 - 19.2]†      | <.001   |
| Urine output, mL         | 1780 [1265 - 2810] | 1483 [1039 - 2346]   | 940 [379 - 1398]*        | <.001   |

### Outcome

|                          | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|--------------------------|------------------|------------------------|--------------------------|---------|
| Duration of initial MV, days | 3 [1 - 7]      | 6 [2 - 9]              | 3.50 [1 - 10]            | .08     |
| Recurrence of MV         | 7 (3.1)         | 4 (8.9)                | 8 (6.6)                  | .11     |
| MV-free daysd            | 83 [39 - 88]    | 81 [30 - 88]           | 19 [1 - 82]†             | <.001   |
| Use of RRT               | 7 (3.1)         | 3 (6.7)                | 55 (45.1)†               | <.001   |
| RRT-free daysd           | 90 [55 - 90]    | 90 [46 - 90]           | 28 [3 - 90]†             | <.001   |

### Complications
d

|                          | No AKI (n = 225) | Transient AKI (n = 45) | Persistent AKI (n = 122) | P Value |
|--------------------------|------------------|------------------------|--------------------------|---------|
| None                     | 199 (88.4)       | 37 (82.2)              | 98 (80.3)                | .11     |
| ICU-acquired AKI         | 17 (7.6)         | 2 (4.4)                | 9 (7.4)                  | .88     |
| ICU-acquired ARDS        | 3 (1.3)          | 1 (2.2)                | 3 (2.5)                  | .54     |
| ICU-acquired infection   | 13 (5.8)         | 6 (13.3)               | 17 (13.9)*               | .20     |
| ICU length of stay, days | 5 [3 - 9]        | 8 [5 - 12]*            | 7 [3 - 13]*              | .001    |
| Hospital length of stay, days | 18 [10 - 36] | 26 [14 - 43]           | 19 [6 - 44]              | .08     |
| ICU-mortality            | 24 (10.7)        | 5 (11.1)               | 48 (39.3)*†              | <.001   |
| 30-day mortality         | 45 (20.0)        | 9 (20.0)               | 58 (47.5)*†              | <.001   |
| 60-day mortality         | 59 (26.2)        | 13 (28.9)              | 62 (50.8)*†              | <.001   |
| 90-day mortality         | 65 (28.9)        | 14 (31.1)              | 66 (54.1)*†              | <.001   |
| 1-year mortality         | 91 (40.4)        | 20 (44.4)              | 73 (59.8)*               | .002    |
| ICU-free daysd           | 81 [39 - 87]     | 79 [25 - 84]           | 23.50 [0 - 81]†          | <.001   |

**Abbreviations:** ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson $\chi^2$ test or the Fisher’s exact test when appropriate. *P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

* Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

b Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

c Other sites of infection: Infections of bones and joints (n=1), Oral infections (n=1), Postoperative wound infections (n=1), Other (n=1)

d Between inclusion and day-90.

* Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### Baseline characteristics and outcomes of patients admitted to the ICU with sepsis and with blood genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury based on a 96-hour cutoff

| Demographics | No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|--------------|-----------------|------------------------|--------------------------|---------|
| Age, years   | 63 [49 - 70]    | 64 [52 - 75]           | 64 [56 - 72]             | .19     |
| Male sex     | 130 (57.8)      | 24 (46.2)              | 68 (59.1)                | .26     |
| Race, white  | 184 (82.5)      | 45 (86.5)              | 98 (87.5)                | .50     |
| Medical admission | 166 (73.8) | 38 (73.1)              | 77 (67.0)                | .41     |

| Chronic comorbidities | No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|------------------------|-----------------|------------------------|--------------------------|---------|
| None                   | 74 (32.9)       | 16 (30.8)              | 41 (35.7)                | .80     |
| Cardiovascular         | 47 (20.9)       | 10 (19.2)              | 28 (24.3)                | .68     |
| Hypertension           | 50 (22.2)       | 19 (36.5)              | 30 (26.1)                | .11     |
| Diabetes               | 37 (16.4)       | 10 (19.2)              | 25 (21.7)                | .47     |
| Liver cirrhosis        | 4 (1.8)         | 1 (1.9)                | 2 (1.7)                  | .99     |
| Immune compromise      | 51 (22.7)       | 11 (21.2)              | 20 (17.4)                | .56     |
| Malignancy             | 50 (22.2)       | 12 (23.1)              | 19 (16.5)                | .43     |

### Charlson comorbidity index

| No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|-----------------|------------------------|--------------------------|---------|
| 3 [1 - 5]       | 3 [2 - 5]              | 3 [2 - 4]                | .80     |

### Chronic medication

| No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|-----------------|------------------------|--------------------------|---------|
| Diuretics       | 44 (19.6)              | 16 (30.8)                | 32 (27.8) | .09     |
| ACE inhibitors / ARBs | 46 (20.4) | 12 (23.1)              | 35 (30.4) | .13     |
| Calcium-entry blockers | 29 (12.9) | 9 (17.3)                | 17 (14.8) | .63     |
| Beta-adrenergetic blockers | 52 (23.1) | 17 (32.7)              | 37 (32.2) | .12     |
| NSAIDs and Cox II inhibitors | 34 (15.1) | 12 (23.1)               | 9 (7.8) | .022    |
| Oral antidiabetic drugs | 20 (8.9) | 9 (17.3)                | 20 (17.4) | .037    |

### Severity at time of admission to ICU

| No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|-----------------|------------------------|--------------------------|---------|
| APACHE IV score | 71 [57 - 89]           | 86 [73 - 102]            | 91 [76 - 117] | <.001   |
| Acute physiology score | 59 [47 - 72] | 70 [61 - 88]            | 79 [63 - 106] | <.001   |
| mSOFA score     | 6 [4 - 8]              | 8 [7 - 10]               | 10 [8 - 13] | <.001   |
| Non-renal mSOFA score | 6 [4 - 7] | 7 [6 - 9]               | 8 [7 - 10] | <.001   |
| Shock            | 91 (40.4)              | 37 (71.2)                | 97 (84.3) | <.001   |
| ARDS             | 63 (28.9)              | 16 (30.8)                | 45 (39.1) | .12     |

### Therapy during the first 24h

| No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|-----------------|------------------------|--------------------------|---------|
| Mechanical ventilation | 194 (86.2) | 44 (84.6)               | 101 (87.8) | .81     |
| Vasopressors    | 130 (57.8)             | 43 (82.7)                | 104 (90.4) | <.001   |
| Dose of vasopressors (mg) | 5.9 [2.3 - 14.4] | 17.1 [3.6 - 35.2]       | 18.6 [9.2 - 38.1] | <.001   |
| Inotropes       | 9 (4.0)                | 7 (13.5)                 | 24 (20.9) | <.001   |
| Dose of inotropes (mg) | 150.2 [75.5 - 344.8] | 143.0 [108.8 - 182.8]   | 102.5 [61.5 - 268.4] | .95     |
| RRT             | 0 (0.0)                | 3 (5.8)                  | 33 (28.7) | <.001   |
| Nephrotoxic drugs (≥ one) | 115 (51.1) | 32 (61.5)               | 93 (80.9) | <.001   |
| Aminoglycoside  | 44 (19.6)              | 15 (28.8)                | 43 (37.4) | .002    |
| Glycopeptide    | 25 (11.1)              | 5 (9.6)                  | 13 (11.3) | >.99    |
| Colloid         | 72 (32.0)              | 25 (48.1)                | 74 (64.3) | <.001   |
| Other           | 11 (4.9)               | 3 (5.8)                  | 7 (6.1) | .81     |

### Source of infection

| No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|-----------------|------------------------|--------------------------|---------|
| Pulmonary tract | 130 (57.8)             | 23 (44.2)                | 42 (36.5) | <.001   |
| Abdominal       | 42 (18.7)              | 17 (32.7)                | 37 (32.2) | .007    |
| Cardiovascular  | 23 (10.2)              | 4 (7.7)                  | 15 (13.0) | .59     |
| Urinary tract   | 12 (5.3)               | 4 (7.7)                  | 10 (8.7) | .44     |
| CNS             | 8 (3.6)                | 0 (0.0)                  | 1 (0.9) | .25     |
| Skin or soft tissue | 8 (3.6) | 2 (3.8)                | 9 (7.8) | .24     |
| Other           | 2 (0.9)                | 2 (3.8)                  | 0 (0.0) | .07     |
| Unknown         | 0 (0.0)                | 0 (0.0)                  | 1 (0.9) | .43     |
## eTable 36 continued

|                                | No AKI (n = 225) | Transient AKI (n = 52) | Persistent AKI (n = 115) | P Value |
|--------------------------------|------------------|------------------------|--------------------------|--------|
| **Renal function during the first 24 hours** |                  |                        |                          |        |
| Creatinine, µmol/L             | 80 [61 - 105]    | 138 [108 - 172]*      | 185 [140 - 246]*†        | <.001  |
| Urea, mmol/L                  | 7.1 [5.1 - 9.9]  | 10.5 [8.3 - 17.3]*     | 13.4 [9.3 - 18.2]*       | <.001  |
| Bicarbonate (minimal), mmol/L  | 21.7 [18.2 - 26.2] | 18.50 [15.9 - 22.4]*   | 16.1 [13.3 - 19.4]*†     | <.001  |
| Urine output, mL              | 1780 [1265 - 2810] | 1450 [1028 - 2358]     | 930 [370 - 1355]*†       | <.001  |
| **Outcome**                   |                  |                        |                          |        |
| Duration of initial MV, days  | 3 [1 - 7]        | 6 [2 - 9]              | 3 [1 - 10]               | .07    |
| Recurrence of MV              | 7 (3.1)          | 4 (7.7)                | 8 (7.0)                  | .13    |
| MV-free days<sup>a</sup>       | 83 [39 - 88]     | 80 [25 - 87]           | 17 [1 - 82]*†            | <.001  |
| Use of RRT                   | 7 (3.1)          | 5 (9.6)                | 53 (46.1)*†              | <.001  |
| RRT-free days<sup>a</sup>      | 90 [55 - 90]     | 90 [38 - 90]           | 26 [3 - 90]*†            | <.001  |
| **Complications**             |                  |                        |                          |        |
| None                          | 199 (88.4)       | 43 (82.7)              | 92 (80.0)                | .09    |
| ICU-acquired AKI              | 17 (7.6)         | 2 (3.8)                | 9 (7.8)                  | .73    |
| ICU-acquired ARDS             | 3 (1.3)          | 2 (3.8)                | 2 (1.7)                  | .39    |
| ICU-acquired infection        | 13 (5.8)         | 7 (13.5)               | 16 (13.9)*†              | .023   |
| ICU length of stay, days      | 5 [3 - 9]        | 8 [6 - 12]*           | 7 [3 - 13]               | <.001  |
| Hospital length of stay, days | 18 [10 - 36]     | 25 [14 - 45]           | 18 [5 - 43]              | .031   |
| ICU-mortality                 | 24 (10.7)        | 6 (11.5)               | 47 (40.9)*†              | <.001  |
| 30-day mortality              | 45 (20.0)        | 12 (23.1)              | 55 (47.6)*†              | <.001  |
| 60-day mortality              | 59 (26.2)        | 16 (30.8)              | 59 (51.3)*†              | <.001  |
| 90-day mortality              | 65 (28.9)        | 17 (32.7)              | 63 (54.8)*†              | <.001  |
| 1-year mortality              | 91 (40.4)        | 24 (46.2)              | 69 (60.0)*               | .003   |
| ICU-free days<sup>a</sup>      | 81 [39 - 87]     | 78 [16 - 84]           | 14 [0 - 81]*†            | <.001  |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Pearson $\chi^2$ test or the Fisher's exact test when appropriate. P value represent comparisons between the three groups.

* Significant vs no AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

<sup>a</sup> Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

<sup>b</sup> Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

<sup>c</sup> Other sites of infection: Infections of bones and joints (n=1), Oral infections (n=1), Postoperative wound infections (n=1), Other (n=1)

<sup>d</sup> Between inclusion and day-90.

<sup>e</sup> Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### eTable 37. Baseline characteristics and outcomes of patients admitted to the ICU for a non-infectious condition and with plasma biomarkers measured upon admission, stratified according to the presence and evolution of acute kidney injury

|                          | No AKI (n = 448) | Transient AKI (n = 39) | Persistent AKI (n = 145) | P Value |
|--------------------------|------------------|------------------------|--------------------------|---------|
| **Demographics**         |                  |                        |                          |         |
| Age, years               | 60 [48 - 69]     | 66 [58 - 76]*          | 66 [55 - 75]*            | <.001   |
| Male sex                 | 290 (64.7)       | 28 (71.8)              | 102 (70.3)               | .38     |
| Race, white              | 393 (87.9)       | 33 (84.6)              | 127 (88.2)               | .81     |
| Medical admission        | 230 (51.3)       | 21 (53.8)              | 81 (55.9)                | .62     |
| **Chronic comorbidities**|                  |                        |                          |         |
| None                     | 166 (37.1)       | 8 (20.5)               | 46 (31.7)                | .08     |
| Cardiovascular compromise| 121 (27.0)       | 11 (28.2)              | 60 (41.4)*               | .005    |
| Hypertension             | 124 (27.7)       | 15 (38.5)              | 43 (29.7)                | .35     |
| Diabetes                 | 62 (13.8)        | 7 (17.9)               | 25 (17.2)                | .48     |
| Liver cirrhosis          | 1 (0.2)          | 0 (0.0)                | 4 (2.8)*                 | .018    |
| Immune compromise        | 40 (8.9)         | 8 (20.5)               | 11 (7.6)                 | .06     |
| Malignancy               | 63 (14.1)        | 6 (15.4)               | 12 (8.3)                 | .16     |
| Charlson comorbidity index| 2 [1 - 4]        | 3 [2 - 5]*             | 3 [2 - 4]*               | <.001   |
| **Chronic medication**   |                  |                        |                          |         |
| Diuretics                | 91 (20.4)        | 7 (17.9)               | 56 (38.9)                | <.001   |
| ACE inhibitors / ARBs    | 114 (25.6)       | 10 (25.6)              | 52 (36.1)                | .049    |
| Calcium-entry blockers   | 53 (11.9)        | 8 (20.5)               | 27 (18.8)                | .05     |
| Beta-adrenergic blockers | 108 (24.2)       | 9 (23.1)               | 55 (38.2)*               | .005    |
| NSAIDs and Cox II inhibitors| 27 (6.1)        | 2 (5.1)                | 11 (7.6)                 | .78     |
| Oral antidiabetic drugs  | 41 (9.2)         | 5 (12.8)               | 19 (13.2)                | .33     |
| Corticosteroids          | 28 (6.3)         | 5 (12.8)               | 9 (6.2)                  | .30     |
| Antiplatelet drugs       | 98 (23.6)        | 13 (34.2)              | 45 (33.6)                | .038    |
| **Severity at time of admission to ICU** | | | | |
| APACHE IV score          | 61 [47 - 81]     | 80 [64 - 113]*         | 92 [73 - 117]*           | <.001   |
| Acute physiology score   | 50 [38 - 70]     | 64 [50 - 100]*         | 79 [60 - 109]*           | <.001   |
| mSOFA score              | 5 [3 - 7]        | 7 [6 - 9]*             | 10 [8 - 11]*             | <.001   |
| Non-renal mSOFA score    | 5 [3 - 6]        | 7 [6 - 8]*             | 7 [6 - 9]*               | <.001   |
| Shock                    | 157 (35.2)       | 20 (51.3)              | 102 (70.3)*              | <.001   |
| ARDS                     | 31 (6.9)         | 3 (7.7)                | 34 (23.4)*               | <.001   |
| **Therapy during the first 24h** | | | | |
| Mechanical ventilation   | 406 (90.6)       | 37 (94.9)              | 130 (89.7)               | .68     |
| Vasopressors             | 282 (62.9)       | 32 (82.1)              | 128 (88.3)*              | <.001   |
| Dose of vasopressors (mg)*| 3.7 [1.3 - 10.4]| 7.9 [1.5 - 14.6]      | 13.8 [4.1 - 29.4]*       | <.001   |
| Inotropes                | 38 (8.5)         | 9 (23.1)*              | 40 (27.6)*               | <.001   |
| Dose of inotropes (mg)*  | 250.6 [109.8 - 483.5] | 257.3 [148.6 - 418.0]| 208.0 [76.4 - 462.9]     | .72     |
| RRT                      | 0 (0.0)          | 0 (0.0)                | 32 (22.1)*               | <.001   |
| Nephrotoxic drugs (≥ one) | 137 (30.6)      | 17 (43.6)              | 69 (47.6)*               | .001    |
| Aminoglycoside           | 8 (1.8)          | 2 (5.1)                | 12 (8.3)*                | .001    |
| Glycopeptide             | 7 (1.6)          | 1 (2.6)                | 12 (8.3)*                | .001    |
| Colloid                  | 89 (19.9)        | 13 (33.3)              | 55 (37.9)*               | <.001   |
| Other                    | 46 (10.3)        | 4 (10.3)               | 7 (4.8)                  | .11     |
| **Renal function during the first 24 hours** | | | | |
| Creatinine, µmol/L       | 80 [66 - 101]    | 118 [101 - 149]*       | 172 [134 - 217]*         | <.001   |
| Urea, mmol/L             | 5.7 [4.0 - 7.5]  | 8.8 [6.0 - 12.4]*      | 10.4 [7.6 - 14.3]*       | <.001   |
| Bicarbonate (minimal), mmol/L | 21.6 [19.4 - 23.9] | 20.4 [17.6 - 22.0] | 17.3 [14.2 - 20.1]*       | <.001   |
| Urine output, mL         | 1875 [1370 - 2773] | 1210 [880 - 2025]* | 865 [365 - 1810]*         | <.001   |
| Outcome | No AKI (n = 448) | Transient AKI (n = 39) | Persistent AKI (n = 145) | P Value |
|---------|-----------------|------------------------|--------------------------|---------|
| Duration of initial MV, days | 2 [1 - 5] | 3 [2 - 6] | 3 [1 - 9]* | .018 |
| Recurrence of MV | 9 (2.0) | 1 (2.6) | 8 (5.5) | .07 |
| MV-free days** | 85 [56 - 88] | 78 [4 - 86]* | 46 [1 - 85]* | <.001 |
| Use of RRT* | 5 (1.1) | 0 (0.0) | 57 (39.3)*† | <.001 |
| RRT-free days** | 90 [90 - 90] | 90 [12 - 90]* | 46 [4 - 90]*† | <.001 |

** Complications

- ICU-acquired AKI: 14 (3.1) vs 1 (2.6) vs 6 (4.1), P = .85
- ICU-acquired ARDS: 16 (3.6) vs 1 (2.6) vs 11 (7.6), P = .11
- ICU-acquired infection: 46 (10.3) vs 2 (5.1) vs 30 (20.7), P = .002

ICU length of stay, days: 4 [2 - 7] vs 5 [4 - 8]* vs 5 [3 - 12]**†, P = .001
Hospital length of stay, days: 14 [7 - 25] vs 14 [8 - 23] vs 15 [5 - 29], P = .96
ICU-mortality: 53 (11.8) vs 9 (23.1)* vs 50 (34.5)*, P < .001
30-day mortality: 92 (20.5) vs 16 (41.0)* vs 62 (42.8)*, P < .001
60-day mortality: 105 (23.4) vs 17 (43.6)* vs 74 (51.0)*, P < .001
90-day mortality: 108 (24.1) vs 18 (46.2)* vs 74 (51.0)*, P < .001
1-year mortality: 141 (31.5) vs 19 (48.7)* vs 84 (57.9)*, P < .001
ICU-free days**: 84 [51 - 87] vs 69 [2 - 83]* vs 28 [0 - 83]*, P < .001

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Fisher’s exact test. P value represent comparisons between the three groups.

* Significant vs No AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.
Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarin, calcineurin inhibitors.
Between inclusion and day-90.
Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
### Medical diagnoses

| Diagnosis                                | N  |
|------------------------------------------|----|
| **Cardiovascular diagnoses**             | 170|
| Cardiac arrest                           | 103|
| Acute myocardial infarction              | 21 |
| Congestive heart failure                 | 11 |
| Cardiogenic shock                        | 10 |
| Rhythm disturbance                       | 9  |
| Cardiomyopathy                           | 6  |
| Embolus, pulmonary                       | 5  |
| Pericardial effusion/tamponade           | 3  |
| Cardiovascular - medical, other          | 3  |
| **Respiratory diagnoses**                | 46 |
| Emphysema/bronchitis                     | 10 |
| Pneumonia, other                         | 10 |
| Pneumonia, aspiration                    | 6  |
| Airway obstruction                       | 5  |
| Respiratory - medical, other             | 4  |
| ARDS                                     | 2  |
| Asthma                                   | 2  |
| Pleural effusions                        | 2  |
| Pneumothorax                             | 2  |
| Respiratory arrest                       | 1  |
| Atelectasis                              | 1  |
|Restrictive lung disease                  | 1  |
| **Neurological diagnoses**               | 40 |
| Subarachnoid hemorrhage                  | 19 |
| Cerebrovascular accident/stroke          | 6  |
| Neurologic - medical, other              | 5  |
| Coma/change in level of consciousness    | 4  |
| Neumor muscular - medical               | 4  |
| Seizures                                 | 2  |
| **Medical, other**                       | 34 |
| Overdose                                 | 6  |
| GI - medical, other                      | 5  |
| GI - medical, other                      | 5  |
| Metabolic/endocrine disorder             | 4  |
| Diabetic ketoacidosis                    | 3  |
| Hematologic disorder                     | 3  |
| Acute hepatic failure                    | 2  |
| Pancreatitis                             | 2  |
| Anaphylaxis                              | 1  |
| Pre-operative hemodynamic monitoring     |    |
| Embolectomy                              |    |
| **Musculoskeletal - medical, other**     | 1  |

### Surgical diagnoses

| Diagnosis                                | N  |
|------------------------------------------|----|
| Abdominal surgery                        | 91 |
| GI cancer                                | 56 |
| GI surgery, other                        | 16 |
| GI Perforation/rupture                   | 5  |
| GI bleeding                              | 5  |
| Genitourinary surgery                    | 4  |
| GI vascular ischemia                     | 3  |
| Cholecystectomy                          | 2  |
| **Cardiothoracic surgery**               | 47 |
| CABG                                     | 13 |
| CABG + valve repair/replacement          | 13 |
| Cardiovascular surgery, other            | 13 |
| Lung/heart transplant                    | 8  |
| **Neurological surgery**                 | 66 |
| Hemorrhage/hematoma                      | 57 |
| Neurologic surgery, other                | 9  |
| **Vascular surgery**                     | 46 |
| Aneurysm                                 | 39 |
| Vascular surgery, other                  | 5  |
| Aorto-femoral bypass graft               | 2  |
| **Surgery, other**                       | 21 |
| Surgery, other                           | 8  |
| Genito-urinary surgery                   | 6  |
| Orthopedic surgery                       | 4  |
| Head & neck cancer                       | 3  |
| **Trauma diagnoses**                     | 71 |
| Trauma                                   | 44 |
| Multiple trauma                          | 15 |
| Head/face trauma                         | 7  |
| Chest/thorax trauma                      | 3  |
| Abdomen/pelvis trauma                    | 2  |

Abbreviations: ARDS, acute respiratory distress syndrome; CABG, coronary artery by-pass graft; GI, gastrointestinal
| Demographics | No AKI (n = 141) | Transient AKI (n = 15) | Persistent AKI (n = 66) | P Value |
|--------------|-----------------|------------------------|--------------------------|---------|
| Age, years   | 60 [48 - 70]    | 64 [57 - 77]           | 69 [59 - 76]             | .002    |
| Male sex     | 85 (60.3)       | 11 (73.3)              | 40 (60.6)                | .66     |
| Race, white  | 125 (89.3)      | 11 (73.3)              | 53 (81.5)                | .10     |
| Medical admission | 73 (51.8)  | 9 (60.0)               | 31 (47.0)                | .62     |
| Chronic comorbidities |         |                       |                          |         |
| None         | 52 (36.9)       | 2 (13.3)               | 17 (25.8)                | .09     |
| Cardiovascular compromise | 30 (21.3) | 7 (46.7)               | 28 (42.4)                | .002    |
| Hypertension | 42 (29.8)       | 9 (60.0)               | 25 (37.9)                | .05     |
| Diabetes     | 26 (18.4)       | 4 (26.7)               | 15 (22.7)                | .56     |
| Liver cirrhosis | 1 (0.7)   | 0 (0.0)                | 2 (3.0)                  | .38     |
| Immune compromise | 17 (12.1) | 1 (6.7)                | 7 (10.6)                 | .94     |
| Malignancy   | 24 (17.0)       | 1 (6.7)                | 8 (12.1)                 | .52     |
| Charlson comorbidity index | 2 [1 - 4]  | 3 [3 - 5]              | 4 [3 - 5]                | .001    |
| Chronic medication |         |                       |                          |         |
| Diuretics    | 32 (22.7)       | 2 (13.3)               | 30 (45.5)                | .002    |
| ACE inhibitors / ARBs | 41 (29.1) | 9 (60.0)               | 32 (48.5)                | .004    |
| Calcium-entry blockers | 18 (12.8) | 3 (20.0)               | 11 (16.7)                | .51     |
| Beta-adrenergic blockers | 34 (24.1) | 5 (33.3)               | 33 (50.0)                | .001    |
| NSAIDs and Cox II inhibitors | 10 (7.1)  | 1 (6.7)                | 6 (9.1)                  | .84     |
| Oral antidiabetic drugs | 16 (11.3) | 3 (20.0)               | 25 (37.9)                | .46     |
| Corticosteroids | 9 (6.4)     | 0 (0.0)                | 4 (6.1)                  | .90     |
| Antiplatelet drugs | 36 (26.9) | 8 (53.3)               | 21 (34.4)                | .09     |
| Severity at time of admission to ICU |          |                       |                          |         |
| APACHE IV score | 59 [46 - 82] | 80 [62 - 117]          | 95 [73 - 132]            | <.001   |
| Acute physiology score | 49 [37 - 71] | 69 [48 - 105] | 79 [60 - 117] | <.001 |
| mSOFA score  | 5 [3 - 7]       | 7 [6 - 9]              | 9 [8 - 12]               | <.001   |
| Non-renal mSOFA score | 5 [3 - 7]  | 6 [5 - 7]              | 7 [6 - 9]                | <.001   |
| Shock        | 61 (43.9)       | 7 (46.7)               | 55 (83.3)                | <.001   |
| ARDS         | 3 (2.1)         | 1 (6.7)                | 11 (16.7)                | <.001   |
| Therapy during the first 24h |          |                       |                          |         |
| Mechanical ventilation | 126 (89.4) | 15 (100.0)             | 60 (90.9)                | .56     |
| Vasopressors | 86 (61.0)       | 11 (73.3)              | 61 (92.4)                | <.001   |
| Dose of vasopressors (mg)* | 7.3 [2.3 - 16.2] | 7.8 [5.9 - 16.4] | 18.1 [7.5 - 35.2] | <.001 |
| Inotropes    | 13 (9.2)        | 4 (26.7)               | 24 (36.4)                | <.001   |
| Dose of inotropes (mg)* | 252.5 [143.3 - 440.2] | 337.7 [210.5 - 492.4] | 242.8 [105.7 - 439.2] | .88     |
| RRT          | 0 (0.0)         | 0 (0.0)                | 14 (21.2)                | <.001   |
| Nephrotoxic drugs (≥ one) | 55 (39.0) | 6 (40.0)               | 38 (57.6)                | .042    |
| Aminoglycoside | 3 (2.1)     | 1 (6.7)                | 4 (6.1)                  | .23     |
| Glycopeptide | 2 (1.4)         | 0 (0.0)                | 5 (7.6)                  | .05     |
| Colloid      | 44 (31.2)       | 6 (40.0)               | 32 (48.5)                | .05     |
| Other a      | 14 (9.9)        | 1 (6.7)                | 4 (6.1)                  | .79     |
| Renal function during the first 24 hours |          |                       |                          |         |
| Creatinine, µmol/L | 81 [64 - 103] | 123 [101 - 168]* | 165 [131 - 212]* | <.001   |
| Urea, mmol/L     | 5.4 [3.9 - 7.1] | 7.9 [5.2 - 14.0]* | 10.2 [8.2 - 15.2]* | <.001   |
| Bicarbonate (minimal), mmol/L | 21.5 [18.6 - 23.8] | 19.4 [18.9 - 21.4] | 16.0 [11.5 - 19.6] | <.001   |
| Urine output, mL | 1765 [1290 - 2600] | 1260 [950 - 2185] | 845 [381 - 1636]* | <.001   |
Table 39 continued

| Outcome                                      | No AKI (n = 141) | Transient AKI (n = 15) | Persistent AKI (n = 66) | P Value |
|----------------------------------------------|------------------|------------------------|-------------------------|---------|
| Duration of initial MV, days                 | 2 [1 - 5]        | 4 [3 - 6]              | 2 [1 - 10]              | .08     |
| Recurrence of MV                            | 2 (1.4)          | 0 (0.0)                | 3 (4.5)                 | .42     |
| MV-free days (c)                             | 85 [27 - 88]     | 80 [3 - 85]            | 51 [1 - 87]*            | .003    |
| Use of RRT                                   | 4 (2.8)          | 0 (0.0)                | 28 (42.4)*†             | <.001   |
| RRT-free days (c)                            | 90 [36 - 90]     | 90 [18 - 90]           | 58 [3 - 90]*            | <.001   |
| Complications (d)                            |                  |                        |                         |         |
| None                                         | 115 (81.6)       | 13 (86.7)              | 46 (69.7)               | .12     |
| ICU-acquired AKI                             | 8 (5.7)          | 0 (0.0)                | 3 (4.5)                 | >.99    |
| ICU-acquired ARDS                            | 7 (5.0)          | 1 (6.7)                | 3 (4.5)                 | .78     |
| ICU-acquired infection                       | 22 (15.6)        | 1 (6.7)                | 18 (27.3)               | .08     |
| ICU length of stay, days                     | 4 [3 - 7]        | 6 [5 - 8]              | 5 [3 - 14]              | .05     |
| Hospital length of stay, days                | 14 [8 - 29]      | 13 [10 - 22]           | 17 [7 - 37]             | .98     |
| ICU-mortality                                | 21 (14.9)        | 3 (20.0)               | 22 (33.3)*              | .009    |
| 30-day mortality                             | 32 (22.7)        | 5 (33.3)               | 21 (31.8)               | .27     |
| 60-day mortality                             | 41 (29.1)        | 5 (33.3)               | 32 (48.5)*              | .023    |
| 90-day mortality                             | 42 (29.8)        | 6 (40.0)               | 32 (48.5)*              | .030    |
| 1-year mortality                             | 55 (39.0)        | 6 (40.0)               | 39 (59.1)*              | .022    |
| ICU-free days (c)                            | 83 [21 - 86]     | 69 [2 - 82]            | 45 [0 - 85]*            | .003    |

Abbreviations: ACE, Angiotensin converting enzyme; AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ARBs, Angiotensin II receptor blockers; CNS, central nervous system; ICU, Intensive care unit; MV, mechanical ventilation; NSAIDs, non-steroidal anti-inflammatory drugs; RRT, renal replacement therapy; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).

Data presented as median [interquartile range], or n (%). Continuous variables were compared using the Kruskal-Wallis test. Associations between categorical variables were tested using the Fisher’s exact test. P value represent comparisons between the three groups.

* Significant vs No AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).
† Significant vs Transient AKI, using a Dunn’s Test of multiple comparisons using rank sums (continuous variables) or a pairwise test for a multi-level 2-dimensional matrix (categorical variables).

a Cumulative dose given for patients who received vasopressors (epinephrine, norepinephrine or dopamine, expressed in norepinephrine-equivalent dose) or dobutamine during the first 24 hours.

b Other nephrotoxic drug; includes any of the following medications: nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, amphotericin B, acyclovir, foscarnet, calcineurin inhibitors.

Between inclusion and day 90.

Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.
**eTable 40. Admission diagnoses of patients admitted to the ICU for a non-infectious condition and with genomic response analyzed upon admission**

| Medical diagnoses                              | N  |
|------------------------------------------------|----|
| **Cardiovascular diagnoses**                   | 57 |
| Cardiac arrest                                 | 37 |
| Acute myocardial infarction                    | 6  |
| Rhythm disturbance                             | 4  |
| Cardiomyopathy                                 | 3  |
| Congestive heart failure                       | 2  |
| Embolus, pulmonary                             | 2  |
| Cardiogenic shock                              | 2  |
| Pericardial effusion/tamponade                 | 1  |
| **Respiratory diagnoses**                      | 18 |
| Emphysema/bronchitis                           | 5  |
| Pneumonia, aspiration                          | 5  |
| Pneumonia, other                               | 4  |
| Airway obstruction                             | 1  |
| ARDS                                           | 1  |
| Restrictive lung disease                       | 1  |
| Respiratory -medical, other                    | 1  |
| **Neurological diagnoses**                     | 13 |
| Subarachnoid hemorrhage                        | 6  |
| Neuromuscular medical                          | 3  |
| Neurologic -medical, other                     | 2  |
| Cerebrovascular accident/stroke                | 2  |
| **Medical, other**                             | 14 |
| Overdose                                       | 3  |
| GI -medical, other                             | 2  |
| Diabetic ketoacidosis                          | 2  |
| Metabolic/endocrine disorder                   | 2  |
| Hematologic disorder                           | 2  |
| Hepatic failure, acute                         | 1  |
| GI Bleeding                                    | 1  |
| Musculoskeletal medical, other                 | 1  |

| Surgical diagnoses                             | N  |
|------------------------------------------------|----|
| **Abdominal surgery**                          | 40 |
| GI cancer                                      | 27 |
| GI surgery, other                              | 6  |
| GI Perforation/rupture                         | 4  |
| GI bleeding                                    | 2  |
| Cholecystectomy                                | 1  |
| **Cardiothoracic surgery**                     | 32 |
| CABG + valve repair/replacement                 | 12 |
| Cardiovascular surgery, other                  | 12 |
| CABG                                           | 7  |
| Lung/heart transplant                          | 1  |
| **Neurological surgery**                       | 8  |
| Hemorrhage/hematoma                            | 8  |
| **Vascular surgery**                           | 12 |
| Aneurysm                                       | 8  |
| Vascular surgery, other                        | 4  |
| **Surgery, other**                             | 5  |
| Surgery, other                                 | 5  |

| Trauma diagnoses                               | N  |
|------------------------------------------------|----|
| Trauma                                         | 23 |
| Multiple trauma                                | 11 |
| Head/face trauma                               | 7  |
| Trauma, other                                  | 3  |
| Chest/thorax trauma                            | 1  |
| Abdomen/pelvis trauma                          | 1  |

Abbreviations: ARDS, acute respiratory distress syndrome; CABG, coronary artery by-pass graft; GI, gastrointestinal
Supplemental figures

*eFigure 1. Flow chart of patient inclusion*

- **Total cohort**
  - (January 2011 - December 2013)
  - 8313 admissions
  - 6992 patients

- **Exclusion:** 5526 admissions
  - No infection upon admission: 5338
  - SOFA score < 2: 885
  - SOFA score NA: 118

- **Sepsis admissions**
  - 2787 admissions
  - 2341 patients

- **Exclusion:** 1242 admissions
  - Readmissions: 798
  - Transfer from another ICU: 203
  - Chronic kidney disease: 395
  - RIFLE score NA: 97

- **Study cohort**
  - 1545 admissions
  - 1545 patients

- **No AKI upon admission**
  - 968 patients

- **AKI upon admission**
  - 577 patients

  - **Transient AKI**
    - 106 patients

  - **Persistent AKI**
    - 471 patients

AKI, acute kidney injury; ICU, Intensive care unit; NA, not available; RIFLE, risk, injury, failure, loss, and end-stage kidney disease; mSOFA, modified Sequential Organ Failure Assessment (excluding central nervous system component).
eFigure 2. Kaplan-Meier 30-day survival plot of patients with sepsis stratified according to the severity of acute kidney injury upon admission to the intensive care unit.

**Number at risk**

|        | 0 - None | R - At risk | I - Injury | F - Failure |
|--------|----------|-------------|------------|-------------|
| Number | 1020     | 170         | 171        | 184         |
|         | 952      | 151         | 146        | 124         |
|         | 895      | 143         | 135        | 143         |
|         | 863      | 134         | 130        | 98          |
|         | 834      | 129         | 125        | 88          |
|         | 822      | 128         | 118        | 85          |
|         | 814      | 126         | 117        | 81          |

RIFLE, risk, injury, failure, loss, and end-stage kidney disease.
eFigure 3. Kaplan-Meier 30-day survival plot of patients with sepsis stratified according to the evolution of acute kidney injury after admission to the intensive care unit.
eFigure 4. Calibration plot for the adjusted logistic regression model predicting 30-day mortality

Calibration plot of the logistic regression model for the prediction of 30-day mortality, after adjustment for age, admission RIFLE score, APACHE acute physiology score, source of infection, and modified-Charlson comorbidity index (omitting the age parameter). The Hosmer-Lemeshow test probability denotes the optimal calibration of the logistic regression model (P>.05)
eFigure 5. Biomarkers of renal function in patients with sepsis during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission

Data are presented as box and whiskers, as specified by Tukey. Dotted lines represent median values obtained in 27 healthy age-matched healthy subjects. Overall P values were derived from the linear mixed model in which the group, or the interaction of time x group (i.e., the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects. Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn's post hoc tests of multiple comparisons using rank sums. * P<.05, ** P<.01, *** P<.001, **** P<.0001. NGAL, Neutrophil gelatinase-associated lipocalin.
eFigure 6. White blood cell counts in patients with sepsis during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury after admission

Data are presented as box and whiskers, as specified by Tukey. Dotted line represents the upper laboratory reference value. Overall P values were derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects. Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn's post hoc tests of multiple comparisons using rank sums. * P < .05, ** P < .01, *** P < .001. AKI, acute kidney injury; WBC, white blood cell.
**eFigure 7. Common transcriptional response in blood leukocytes obtained on admission in sepsis patients without, transient or persistent acute kidney injury**

Considering Benjamini-Hochberg's adjusted $P < 0.05$, over-expressed (orange, top), and under-expressed (blue, bottom) genes were analyzed for association with canonical signaling pathways by Ingenuity pathway analysis (IPA, www.ingenuity.com). Significance was gauged by BH-adjusted Fisher exact probability. $-\log (BH) P$, negative log transformed BH-adjusted $P$ value.
Considering Benjamini-Hochberg’s adjusted $P<.05$, over-expressed (orange, top), and under-expressed (blue, bottom) genes were analyzed for association with canonical signaling pathways by Ingenuity pathway analysis (IPA, www.ingenuity.com). Significance was gauged by BH-adjusted Fisher exact probability. $-\log (BH) P$, negative log transformed BH-adjusted $P$-value.
eFigure 9. Kaplan-Meier survival plots of patients with sepsis still present in the intensive care unit on day 4, stratified according to severity and evolution of acute kidney injury

Kaplan-Meier 30-day survival plots according to (a) the severity upon admission and (b) the evolution of acute kidney injury, in the subgroup of patients still present in the ICU on day 4.
eFigure 10. Kaplan-Meier 30-day survival plot of patients with septic shock stratified according to the evolution of acute kidney injury after admission to the intensive care unit.
eFigure 11. Leukocyte genomic responses upon admission in patients admitted with septic shock without, transient, or persistent acute kidney injury

- No AKI vs. healthy
- Transient AKI vs. healthy
- Persistent AKI vs. healthy

- Underexpressed genes (adj. p<0.05, fold expression < -1.5)
- Overexpressed genes (adj. p<0.05, fold expression > 1.5)
**eFigure 11. Leukocyte genomic responses upon admission in patients admitted with septic shock without, transient, or persistent acute kidney injury (Legend)**

(a) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with septic shock without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient AKI and healthy subjects (center), and between patients with persistent AKI and healthy subjects (right). Considering adjusted P<0.05, 9106, 8001 and 9457 genes were identified as differentially expressed in patients without AKI, patients with transient AKI and patients with persistent AKI on admission vs healthy subjects, respectively. Blue dots represent significantly underexpressed genes (adjusted P<0.05, fold expression < -1.5) whereas red dots represent significantly overexpressed genes (adjusted P<0.05, fold expression > 1.5) in patients relative to healthy controls. Horizontal dotted line indicates multiple-test adjusted Benjamini-Hochberg (BH) P<0.05 threshold. Within plots, pie charts show the extent of gene expression changes: blue slices show significantly underexpressed genes (adjusted P<0.05 and expression more than 1.5-times decreased compared with healthy controls), red slices show significantly overexpressed genes (adjusted P<0.05 and expression more than 1.5-time increased compared with healthy controls), and grey slices show significantly different gene expression (adjusted P<0.05 and expression less than 1.5-time increased or decreased compared with healthy controls). (b) Venn-Euler representation of differentially expressed genes on admission in patients admitted with septic shock without, transient or persistent AKI vs healthy subjects (adjusted P<0.05). Red arrows denote overexpressed genes, blue arrows denote underexpressed genes. (c) Dot plot depicting the common response (log2 fold changes) of patients without, transient or persistent AKI, or without AKI as compared with healthy subjects. Rho, Spearman’s correlation coefficient. (d) Volcano plot illustrating the differences in leukocyte genomic responses on admission between patients with transient AKI relative to patients without AKI (left), between patients with persistent AKI relative to patients without AKI (center), and between patients with persistent AKI relative to patients with transient AKI (right). Considering adjusted P<0.05, 30 genes were differentially expressed in patients with persistent AKI vs no AKI. No gene was differentially expressed in patients with transient vs. no AKI and in patients with persistent vs. transient AKI. Within plots, pie charts show the extent of gene expression changes compared to the control group.
eFigure 12. Leukocyte genomic responses upon admission in patients admitted with septic shock of short duration (< 52 hours) without, transient, or persistent acute kidney injury
eFigure 12. Leukocyte genomic responses upon admission in patients admitted with septic shock of short duration (< 52 hours) without, transient, or persistent acute kidney injury (Legend)

(a) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with septic shock of short duration (52 hours) without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient AKI and healthy subjects (center), and between patients with persistent AKI and healthy subjects (right). Considering adjusted $P<0.05$, 9006, 6900 and 8802 genes were identified as differentially expressed in patients without AKI, patients with transient AKI and patients with persistent AKI on admission vs healthy subjects, respectively. Blue dots represent significantly underexpressed genes (adjusted $P<0.05$, fold expression $<1.5$) whereas red dots represent significantly overexpressed genes (adjusted $P<0.05$, fold expression $>1.5$) in patients relative to healthy controls. Horizontal dotted line indicates multiple-test adjusted Benjamini-Hochberg (BH) $P<0.05$ threshold. Within plots, pie charts show the extent of gene expression changes: blue slices show significantly underexpressed genes (adjusted $P<0.05$ and expression more than 1.5-times decreased compared with healthy controls), red slices show significantly overexpressed genes (adjusted $P<0.05$ and expression more than 1.5-time increased compared with healthy controls), and grey slices show significantly different gene expression (adjusted $P<0.05$ and expression less than 1.5-time increased or decreased compared with healthy controls). (b) Venn-Euler representation of differentially expressed genes on admission in patients admitted with septic shock of short duration (52 hours) without, transient or persistent AKI vs healthy subjects (adjusted $P<0.05$). Red arrows denote overexpressed genes, blue arrows denote underexpressed genes. (c) Dot plot depicting the common response (log2 fold changes) of patients without, transient or persistent AKI, or without AKI as compared with healthy subjects. Rho, Spearman's correlation coefficient. (d) Volcano plot illustrating the differences in leukocyte genomic responses on admission between patients with transient AKI relative to patients without AKI (left), between patients with persistent AKI relative to patients without AKI (center), and between patients with persistent AKI relative to patients with transient AKI (right). Considering adjusted $P<0.05$, 45 genes were differentially expressed in patients with persistent AKI vs no AKI. No gene was differentially expressed in patients with transient vs. no AKI and in patients with persistent vs. transient AKI. Within plots, pie charts show the extent of gene expression changes compared to the control group.
eFigure 13. Leukocyte genomic responses upon admission in patients admitted with septic shock of long duration (≥ 52 hours) without, transient, or persistent acute kidney injury
**eFigure 13. Leukocyte genomic responses upon admission in patients admitted with septic shock of long duration (≥ 52 hours) without, transient, or persistent acute kidney injury (Legend)**

(a) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with septic shock of long duration (≥ 52 hours) without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient AKI and healthy subjects (center), and between patients with persistent AKI and healthy subjects (right). Considering adjusted $P<.05$, 8378, 7417 and 9350 genes were identified as differentially expressed in patients without AKI, patients with transient AKI and patients with persistent AKI on admission vs healthy subjects, respectively. Blue dots represent significantly underexpressed genes (adjusted $P<.05$, fold expression $<-1.5$) whereas red dots represent significantly overexpressed genes (adjusted $P<.05$, fold expression $>1.5$) in patients relative to healthy controls. Horizontal dotted line indicates multiple-test adjusted Benjamini-Hochberg (BH) $P<.05$ threshold. Within plots, pie charts show the extent of gene expression changes: blue slices show significantly underexpressed genes (adjusted $P<.05$ and expression more than 1.5-times decreased compared with healthy controls), red slices show significantly overexpressed genes (adjusted $P<.05$ and expression more than 1.5-time increased compared with healthy controls), and grey slices show significantly different gene expression (adjusted $P<.05$ and expression less than 1.5-time increased or decreased compared with healthy controls). (b) Venn-Euler representation of differentially expressed genes on admission in patients admitted with septic shock of long duration (≥ 52 hours) without, transient or persistent AKI vs healthy subjects (adjusted $P<.05$). Red arrows denote overexpressed genes, blue arrows denote underexpressed genes. (c) Dot plot depicting the common response (log2 fold changes) of patients without, transient or persistent AKI, or without AKI as compared with healthy subjects. Rho, Spearman’s correlation coefficient. (d) Volcano plot illustrating the differences in leukocyte genomic responses on admission between patients with transient AKI relative to patients without AKI (left), between patients with persistent AKI relative to patients without AKI (center), and between patients with persistent AKI relative to patients with transient AKI (right). Considering adjusted $P<.05$, no gene was differentially expressed.
**eFigure 14.** Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury (RIFLE I and F only)

(a) Comparison of leukocyte genomic responses between patients with no AKI, transient AKI, and persistent AKI vs. healthy controls.

- **Underexpressed genes** (adj. p<0.05, fold expression < -1.5)
- **Overexpressed genes** (adj. p<0.05, fold expression > 1.5)

(b) Venn diagram showing unique and common gene sets across different AKI categories.

(c) Scatter plots illustrating the correlation between AKI severity and gene expression changes.

- **rho** values: 0.97, 0.98

(d) Additional scatter plots comparing transient vs. no AKI and persistent vs. no AKI.

- **Underexpressed genes** (adj. p<0.05, fold expression < -1.5)
- **Overexpressed genes** (adj. p<0.05, fold expression > 1.5)
**eFigure 14** Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury (RIFLE I and F only) (Legend)

(a) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with sepsis without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient AKI and healthy subjects (center), and between patients with persistent AKI and healthy subjects (right). Of AKI patients, only those with a I or F RIFLE score upon admission have been included. Considering adjusted $P < 0.05$, 9040, 6387 and 9366 genes were identified as differentially expressed in patients without AKI, patients with transient AKI and patients with persistent AKI on admission vs healthy subjects, respectively. Blue dots represent significantly underexpressed genes (adjusted $P < 0.05$, fold expression $<-1.5$) whereas red dots represent significantly overexpressed genes (adjusted $P < 0.05$, fold expression $>1.5$) in patients relative to healthy controls. Horizontal dotted line indicates multiple-test adjusted Benjamini-Hochberg (BH) $P < 0.05$ threshold. Within plots, pie charts show the extent of gene expression changes: blue slices show significantly underexpressed genes (adjusted $P < 0.05$ and expression more than 1.5-times decreased compared with healthy controls), red slices show significantly overexpressed genes (adjusted $P < 0.05$ and expression more than 1.5-time increased compared with healthy controls), and grey slices show significantly different gene expression (adjusted $P < 0.05$ and expression less than 1.5-time increased or decreased compared with healthy controls). (b) Venn-Euler representation of differentially expressed genes on admission in patients admitted with sepsis without, transient or persistent RIFLE I and F only) AKI vs healthy subjects (adjusted $P < 0.05$). Red arrows denote overexpressed genes, blue arrows denote underexpressed genes. (c) Dot plot depicting the common response (log2 fold changes) of patients without, transient or persistent AKI, or without AKI as compared with healthy subjects. Rho, Spearman’s correlation coefficient. (d) Volcano plot illustrating the differences in leukocyte genomic responses on admission between patients with transient AKI relative to patients without AKI (left), between patients with persistent AKI relative to patients without AKI (center), and between patients with persistent AKI relative to patients with transient AKI (right). Considering adjusted $P < 0.05$, 2429 genes were differentially expressed in persistent AKI vs. no AKI. No gene was differentially expressed in transient vs. no AKI and persistent vs. transient AKI.
eFigure 15. Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury based on a 72-hour cutoff

- Underexpressed genes (adj. p<0.05, fold expression < -1.5)
- Overexpressed genes (adj. p<0.05, fold expression > 1.5)
**eFigure 15. Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury based on a 72-hour cutoff**

*(Legend)*

(a) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with sepsis without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient AKI and healthy subjects (center), and between patients with persistent AKI and healthy subjects (right), with persistent defined as remaining present beyond 72 hours from AKI onset. Considering adjusted $P<.05$, 9037, 8485 and 9486 genes were identified as differentially expressed in patients without AKI, patients with transient AKI and patients with persistent AKI on admission vs healthy subjects, respectively. Blue dots represent significantly underexpressed genes (adjusted $P<.05$, fold expression $<1.5$) whereas red dots represent significantly overexpressed genes (adjusted $P<.05$, fold expression $>1.5$) in patients relative to healthy controls. Horizontal dotted line indicates multiple-test adjusted Benjamini-Hochberg (BH) $P<.05$ threshold. Within plots, pie charts show the extent of gene expression changes: blue slices show significantly underexpressed genes (adjusted $P<.05$ and expression more than 1.5-times decreased compared with healthy controls), red slices show significantly overexpressed genes (adjusted $P<.05$ and expression more than 1.5-time increased compared with healthy controls), and grey slices show significantly different gene expression (adjusted $P<.05$ and expression less than 1.5-time increased or decreased compared with healthy controls). (b) Venn-Euler representation of differentially expressed genes on admission in patients admitted with sepsis without, transient or persistent (>72 hours) AKI vs healthy subjects (adjusted $P<.05$). Red arrows denote overexpressed genes, blue arrows denote underexpressed genes. (c) Dot plot depicting the common response (log2 fold changes) of patients without, transient or persistent AKI, or without AKI as compared with healthy subjects. Rho, Spearman’s correlation coefficient. (d) Volcano plot illustrating the differences in leukocyte genomic responses on admission between patients with transient AKI relative to patients without AKI (left), between patients with persistent AKI relative to patients without AKI (center), and between patients with persistent AKI relative to patients with transient AKI (right). Considering adjusted $P<.05$, 229 and 2426 genes were differentially expressed in transient and persistent AKI vs. no AKI, respectively. No gene was differentially expressed in persistent vs. transient AKI.
eFigure 16. Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury based on a 96-hour cutoff.
Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury based on a 96-hour cutoff (Legend)

(a) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with sepsis without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient AKI and healthy subjects (center), and between patients with persistent AKI and healthy subjects (right), with persistent defined as remaining present beyond 96 hours from AKI onset. Considering adjusted $P<.05$, 9036, 8685 and 9432 genes were identified as differentially expressed in patients without AKI, patients with transient AKI and patients with persistent AKI on admission vs healthy subjects, respectively. Blue dots represent significantly underexpressed genes (adjusted $P<.05$, fold expression $<-1.5$) whereas red dots represent significantly overexpressed genes (adjusted $P<.05$, fold expression $>1.5$) in patients relative to healthy controls. Horizontal dotted line indicates multiple-test adjusted Benjamini-Hochberg (BH) $P<.05$ threshold. Within plots, pie charts show the extent of gene expression changes: blue slices show significantly underexpressed genes (adjusted $P<.05$ and expression more than 1.5-times decreased compared with healthy controls), red slices show significantly overexpressed genes (adjusted $P<.05$ and expression more than 1.5-time increased compared with healthy controls), and grey slices show significantly different gene expression (adjusted $P<.05$ and expression less than 1.5-time increased or decreased compared with healthy controls). (b) Venn-Euler representation of differentially expressed genes on admission in patients admitted with sepsis without, transient or persistent (>96 hours) AKI vs healthy subjects (adjusted $P<.05$). Red arrows denote overexpressed genes, blue arrows denote underexpressed genes. (c) Dot plot depicting the common response (log2 fold changes) of patients without, transient or persistent AKI, or without AKI as compared with healthy subjects. Rho, Spearman’s correlation coefficient. (d) Volcano plot illustrating the differences in leukocyte genomic responses on admission between patients with transient AKI relative to patients without AKI (left), between patients with persistent AKI relative to patients without AKI (center), and between patients with persistent AKI relative to patients with transient AKI (right). Considering adjusted $P<.05$, 274 and 2157 genes were differentially expressed in transient and persistent AKI vs. no AKI, respectively. No gene was differentially expressed in persistent vs. transient AKI.
**eFigure 17. Biomarkers of renal function in patients admitted for non-infectious conditions during the first 4 days of ICU stay, stratified according to the evolution of acute kidney injury**

Data are presented as box and whiskers, as specified by Tukey. Dotted lines represent median values obtained in 27 healthy age-matched healthy subjects. Overall *P* values were derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects. Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn's post hoc tests of multiple comparisons using rank sums. * *P*<.05, ** *P*<.01, *** *P*<.001, **** *P*<.0001. NGAL, Neutrophil gelatinase-associated lipocalin.
eFigure 18. Host response biomarkers in patients admitted for non-infectious conditions during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury

**a** Inflammatory responses

- IL-10
- IL-6
- IL-8
- MMP-8

**b** Endothelial cell activation

- E-Selectin
- aCAM-1
- Angioprotein-1
- ANG-2, ANG-1

**C** Coagulation activation

- D-dimer
- Protein C
- Antithrombin
**eFigure 18. Host response biomarkers in patients admitted for non-infectious conditions during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury (legend)**

Biological parameters are classified as (a) inflammatory responses, (b) endothelial cell activation, and (c) coagulation activation biomarkers. Data are presented as box and whiskers, as specified by Tukey. Dotted lines represent median values obtained in 27 healthy age-matched healthy subjects. Overall P values were derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific intercept and slopes were defined as random effects. Comparisons between groups at specific days were performed using the Kruskal-Wallis test followed by Dunn's post hoc tests of multiple comparisons using rank sums. * P<.05, ** P<.01, *** P<.001, **** P<.0001. AKI, acute kidney injury; ANG, angiopoietin; aPTT, activated partial thromboplastin time; IL, interleukin; MMP, matrix metalloproteinase; PT, prothrombin time; sE-Selectin, soluble E-selectin; sICAM, soluble intercellular adhesion molecule
eFigure 19. Leukocyte genomic responses upon admission in patients admitted for non-infectious conditions without, transient, or persistent acute kidney injury

- Underexpressed genes (adj. p<0.05, fold expression < -1.5)
- Overexpressed genes (adj. p<0.05, fold expression > 1.5)
eFigure 19. Leukocyte genomic responses upon admission in patients admitted for non-infectious conditions without, transient, or persistent acute kidney injury (Legend)

(a) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted for a non-infectious condition without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient AKI and healthy subjects (center), and between patients with persistent AKI and healthy subjects (right). Considering adjusted $P < 0.05$, 9152, 8279 and 9494 genes were identified as differentially expressed in patients without AKI, patients with transient AKI and patients with persistent AKI on admission vs healthy subjects, respectively. Blue dots represent significantly underexpressed genes (adjusted $P < 0.05$, fold expression $< -1.5$) whereas red dots represent significantly overexpressed genes (adjusted $P < 0.05$, fold expression $> 1.5$) in patients relative to healthy controls. Horizontal dotted line indicates multiple-test adjusted Benjamini-Hochberg (BH) $P < 0.05$ threshold. Within plots, pie charts show the extent of gene expression changes: blue slices show significantly underexpressed genes (adjusted $P < 0.05$ and expression more than 1.5-times decreased compared with healthy controls), red slices show significantly overexpressed genes (adjusted $P < 0.05$ and expression more than 1.5-time increased compared with healthy controls), and grey slices show significantly different gene expression (adjusted $P < 0.05$ and expression less than 1.5-time increased or decreased compared with healthy controls).

(b) Venn-Euler representation of differentially expressed genes on admission in patients admitted for a non-infectious condition without, transient or persistent AKI vs healthy subjects (adjusted $P < 0.05$). Red arrows denote overexpressed genes, blue arrows denote underexpressed genes.

(c) Dot plot depicting the common response (log2 fold changes) of patients without, transient or persistent AKI, or without AKI as compared with healthy subjects. Rho, Spearman’s correlation coefficient.

(d) Volcano plot illustrating the differences in leukocyte genomic responses on admission between patients with transient AKI relative to patients without AKI (left), between patients with persistent AKI relative to patients without AKI (center), and between patients with persistent AKI relative to patients with transient AKI (right). Considering adjusted $P < 0.05$, 358 and 1778 genes were differentially expressed in patients with transient AKI and in patients with persistent AKI vs no AKI, respectively. No gene was differentially expressed in patients with persistent vs. transient AKI. Within plots, pie charts show the extent of gene expression changes compared to the control group.
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