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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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
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		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	9 +supplemental eMethods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	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
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Study size	10	Explain how the study size was arrived at	7
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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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*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 (hyperkaliemia, 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/). 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 Benjamini-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) 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]

	GFR criteria			Urine output criteria
	RIFLE		KDIGO	(both scores)
Risk	Increased sCreat x1.5 or GFR decrease > 25 percent	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 percent	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 Acute rise ≥0.5 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.

eTable 2. Baseline characteristics and outcomes of patients admitted to the ICU with sepsis, stratified according to the study center

	AMC (n= 890)	UMCU (n= 655)	*P* Value
Demographics			
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			
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 (15.6)	157 (24.0)	<.001
Malignancy	137 (15.4)	197 (30.1)	<.001
Charlson comorbidity index	3 [1 - 4]	4 [2 - 5]	<.001
Chronic medication			
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
Antiplatelet drugs	184 (22.2)	160 (24.4)	.32
Severity at time of admission to ICU			
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			
Mechanical ventilation	687 (77.2)	571 (87.2)	<.001
Vasopressors	602 (67.6)	377 (57.6)	<.001
Dose of Vasopressors (mg)[a]	8.9 [2.9 - 20]	9.4 [3.7 - 19.2]	.84
Inotropes	58 (6.5)	74 (11.3)	.001
Dose of inotropes (mg)[a]	165.3 [73.3 - 277.2]	151.5 [53.8 - 310.2]	.89
RRT	82 (9.2)	25 (3.8)	<.001
Nephrotoxic drugs (≥ one)	548 (61.6)	168 (25.6)	<.001
Aminoglycoside	258 (29.0)	23 (3.5)	<.001
Glycopeptide	156 (17.5)	40 (6.1)	<.001
Colloid	314 (35.3)	54 (8.2)	<.001
Other[b]	66 (7.4)	75 (11.5)	.007
Source of infection			
Pulmonary tract	431 (48.4)	349 (53.3)	.06
Abdominal	185 (20.8)	105 (16.0)	.021
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
Other[c]	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	129 (14.5)	64 (9.8)	.006
RRT-free days[d]	90 [17 - 90]	90 [20 - 90]	.44
Complications[e]			
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.

[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.

eTable 3. Causative pathogens in patients admitted with sepsis stratified according to the presence and evolution of acute kidney injury

	No AKI (n = 968)	AKI		*P* Value
		Transient AKI (n = 106)	Persistent AKI (n = 471)	
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[a]	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.

[a] 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 (95% CI)	*P* Value	Wald test χ2 (df), *P*
Crude model[a]			
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[b]			
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).

eTable 5. 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

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 67)	Persistent AKI (n = 302)	
Demographics				
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
Antiplatelet drugs	101 (21.7)	14 (21.2)	76 (26.0)	.36
Severity at time of admission to ICU				
APACHE IV score	69 [54-88]	75 [65-93]*	96 [76-118]*†	<.001
Acute physiology score	57 [44-71]	64 [55-78]*	81 [63-105]*†	<.001
mSOFA score	6 [4-8]	8 [6-9]*	10 [7-12]*†	<.001
Non-renal mSOFA score	6 [4-7]	7 [5-8]*	8 [6-10]*†	<.001
Shock	209 (42.1)	42 (62.7)*	233 (77.2)*	<.001
ARDS	144 (29.0)	23 (34.3)	108 (35.8)	.12
Therapy during the first 24h				
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

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 67)	Persistent AKI (n = 302)	
Renal function during the first 24 hours				
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[b]	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[d]	90 [44-90]	90 [40-90]	63 [4-90]*†	<.001
Complications[e]				
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[d]	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.

eTable 6. 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

eTable 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.

eTable 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)	AKI		*P* Value
		Transient AKI (n = 36)	Persistent AKI (n = 131)	
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)	8 (22.2)	30 (22.9)	.90
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[b]	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[c]	2 (0.9)	2 (5.6)	0 (0.0)	.05
Unknown	0 (0.0)	0 (0.0)	1 (0.8)	.43

eTable 8 continued

	No AKI (n = 225)	AKI		*P* Value
		Transient AKI (n = 36)	Persistent AKI (n = 131)	
Renal function during the first 24 hours				
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 [13.3-19.7]*†	<.001
Urine output, mL	1780 [1265-2810]	1595 [1068-2388]	965 [420-1413]*†	<.001
Outcome				
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]				
None	199 (88.4)	29 (80.6)	106 (80.9)	.11
ICU-acquired AKI	17 (7.6)	2 (5.6)	9 (6.9)	.90
ICU-acquired ARDS	3 (1.3)	1 (2.8)	3 (2.3)	.72
ICU-acquired infection	13 (5.8)	5 (13.9)	18 (13.7)	.025
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 [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).

[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).

eTable 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)	AKI		*P* Value
		Transient AKI (n = 83)	Persistent AKI (n = 300)	
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 compromise	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 [58-91]	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[b]	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

	No AKI (n = 543)	AKI		*P* Value
		Transient AKI (n = 83)	Persistent AKI (n = 300)	
Renal function during the first 24 hours				
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[e]				
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[d]	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).

[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] 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).

[d] Between inclusion and day-90.

[e] 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 (95% CI)	P Value	Wald test χ2 (df), *P*	Odds Ratio (95% CI)	P Value	Wald test χ2 (df), *P*
Crude model[a]						
No AKI	1.00 (reference)	-	19.4 (2), *P*<.001	1.00 (reference)	-	23.8 (2) *P*<.001
Transient AKI	1.05 (0.60-1.82)	.87		1.15 (0.72-1.83)	.57	
Persistent AKI	1.98 (1.45-2.71)	<.001		2.03 (1.52-2.70)	<.001	
Adjusted model[b]						
No AKI	1.00 (reference)	-	5.76 (2), *P*=.056	1.00 (reference)	-	5.64 (2) *P*=.06
Transient AKI	1.65 (0.74-3.66)	.22		1.55 (0.73-3.29)	.26	
Persistent AKI	2.24 (1.15-4.34)	.018		2.16 (1.12-4.17)	.021	

[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).

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)	AKI		*P* Value
		Transient AKI (n = 54)	Persistent AKI (n = 116)	
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)[a]	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)[a]	151.4 [26.3 - 349.2]	218.3 [180.7 - 566.5]	225.5 [150.6 - 356.9]	.62
RRT	2 (1.2)	3 (5.6)	18 (15.7)*	<.001
Nephrotoxic 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 [b]	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[c]	6 (3.7)	2 (3.7)	3 (2.6)	.85
Unknown	0 (0.0)	0 (0.0)	1 (0.9)	.51

eTable 12 continued

	No AKI (n = 162)	AKI		*P* Value
		Transient AKI (n = 54)	Persistent AKI (n = 116)	
Renal function during the first 24 hours				
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				
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[e]				
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-renal 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 $\chi 2$ 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), 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			*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)		
Inflammatory responses											
IL-10 (pg/mL)	9.8 [3.7-29.7]	19.6 [7.9-49.8]*	26.3 [8.5-108.0]*	7.3 [3.2-14.0]	7.6 [3.7-14.4]	12.9 [4.3-42.1]*	5.1 [2.4-11.4]	4.5 [2.8-6.9]	9.0 [3.5-31.4]*†	<.001	.031
IL-6 (pg/mL)	184.3 [43.6-921.9]	288.2 [75.0-1403.7]	408.7 [77.2-2063.3]	76.3 [21.2-245.0]	103.7 [25.4-197.8]	86.1 [30.1-370.0]	47.3 [13.5-168.8]	26.4 [11.1-75.0]	50.2 [15.9-99.0]	.19	.049
IL-8 (pg/mL)	107.4 [37.7-346.4]	158.1 [71.4-567.6]	185.6 [81.0-760.8]*	62.9 [28.1-149.9]	86.2 [30.5-172.6]	127.2 [60.0-372.9]*†	51.1 [23.4-134.5]	57.5 [31.5-72.7]	90.5 [43.8-215.2]*†	.001	.20
MMP-8 (ng/mL)	2.6 [0.9-7.7]	7.0 [2.4-16.2]*	5.6 [1.9-15.5]*	1.7 [0.5-5.2]	2.7 [1.2-8.8]	2.5 [1.0-8.2]	1.2 [0.4-3.6]	1.3 [0.7-3.6]	2.1 [1.2-6.1]*	.001	.10
Endothelial cell activation											
Fractalkine (pg/mL)	22.2 [13.4-53.8]	32.3 [14.7-67.3]	32.0 [17.3-83.1]*	19.7 [12.8-40.1]	29.5 [12.8-61.4]	34.3 [15.8-80.2]*	21.7 [13.4-73.6]	27.3 [15.3-55.6]	44.2 [28.5-93.7]*	.005	.043
sE-Selectin (ng/mL)	8.6 [4.4-21.4]	12.3 [5.0-32.3]	13.0 [5.4-26.8]	10.0 [4.1-17.9]	10.0 [4.4-22.4]	9.7 [3.9-19.5]	9.2 [3.4-19.3]	9.4 [4.0-15.3]	8.6 [4.2-16.4]	.32	.08
sICAM-1 (ng/mL)	184.4 [96.9-320.6]	148.2 [93.1-277.0]	197.6 [108.7-310.5]	205.8 [109.9-338.7]	168.3 [115.7-299.4]	218.6 [124.6-355.4]	241.9 [146.2-363.5]	169.6 [111.9-326.1]	247.1 [162.9-376.6]	.29	.56
Angiopoietin-1 (ng/mL)	2.6 [0.9-6.6]	3.4 [1.1-8.6]	2.5 [1.0-5.5]	1.9 [0.8-4.9]	2.0 [0.9-3.9]	1.1 [0.6-2.9]*	1.7 [0.7-4.3]	2.1 [1.1-4.8]	1.1 [0.5-3.0]†	.13	.11
Angiopoietin-2 (ng/mL)	7.3 [2.8-13.1]	7.8 [3.2-15.9]	10.0 [4.5-22.7]*	6.8 [3.7-14.5]	9.4 [3.8-19.9]	12.0 [4.6-26.7]*	6.8 [3.2-12.0]	5.4 [3.4-8.0]	7.9 [4.1-15.2]†	.18	.68
ANG-2:ANG-1	2.2 [0.6-9.2]	2.2 [0.7-7.2]	4.5 [0.9-19.3]	3.6 [1.1-12.0]	4.3 [1.7-15.5]	9.5 [2.7-28.4]*	3.5 [0.9-10.8]	2.6 [0.7-6.0]*	7.8 [2.5-20.4]*	.07	.69

eTable 13 continued

	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)		
Coagulation activation											
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]†	.001	.54
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]	0.13	0.86
Antithrombin (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]	.93	.20
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]	.036	.36
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]	.021	.73
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 [67.0-253.0]	168.0 [80.8-226.0]	128.5 [53.5-194.5]	.14	.63

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

eTable 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

	No AKI (n = 362)	AKI		*P* Value
		Transient AKI (n = 73)	Persistent AKI (n = 349)	
Demographics				
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)[a]	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)[a]	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 [b]	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[c]	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)	AKI		*P* Value
		Transient AKI (n = 42)	Persistent AKI (n = 233)	
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 days[d]	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 days[d]	90 [36 - 90]	90 [46 - 90]	31 [2 - 90]*†	<.001
Complications[e]				
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 days[d]	80 [19 - 86]	81 [37 - 86]	12 [0 - 80]*†	<.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), Postoperative wound infections (n= 11), Upper respiratory tract infections (n= 4), Viral systemic infections (n=3), other (n= 12).

[d] Between inclusion and day-90.

[e] Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.

eTable 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)	.26
Beta-adrenergic blockers	168 (25.3)	42 (34.7)	.035
NSAIDs and Cox II inhibitors	79 (11.9)	12 (9.9)	.64
Oral antidiabetic drugs	90 (13.6)	15 (12.4)	.89
Corticosteroids	65 (9.8)	11 (9.1)	>.99
Antiplatelet drugs	155 (24.3)	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 - 21.2]	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
Other[b]	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
Other[c]	34 (5.1)	4 (3.3)	.50
Unknown	5 (0.8)	2 (1.7)	.30

eTable 15 continued

	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]	.001
CVP, mmHg	12 [8 - 16]	14 [9.8 - 19.3]	.001
Creatinine (µmol/L)	116 [79 - 170]	157 [108 - 206]	<.001
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]	<.001
Urine output, mL	1380 [833 - 2330]	1005 [405 - 1745]	<.001
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[d]	78 [3 - 87]	18 [1 - 83]	<.001
Use of RRT	120 (18.1)	42 (34.7)	<.001
RRT-free days[d]	90 [10 - 90]	46 [2 - 90]	<.001
Complications[e]			
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[d]	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.

[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).

eTable 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)	AKI		*P* Value
		Transient AKI (n = 42)	Persistent AKI (n = 233)	
Demographics				
Age, years	61 [48 - 70]	63 [52 - 72]	64 [54 - 72]*	.022
Male sex	126 (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 compromise	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	21 (10.0)	7 (16.7)	32 (13.7)	.31
Corticosteroids	29 (13.9)	4 (9.5)	22 (9.4)	.32
Antiplatelet drugs	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)	.89
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 - 332.6]	.84
RRT	3 (1.4)	3 (7.1)	65 (28.0)*†	<.001
Nephrotoxic 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
Other[b]	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
Other[c]	4 (1.9)	1 (2.4)	6 (2.6)	.90
Unknown	0 (0.0)	0 (0.0)	5 (2.1)	.14

eTable 16 continued

	No AKI	AKI	*P* Value

	(n = 209)	Transient AKI (n = 42)	Persistent AKI (n = 233)	
Renal function during the first 24 hours				
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 [13.0 - 18.6]*†	<.001
Urine output, mL	1760 [1270 - 2640]	1398 [931 - 2369]	880 [395 - 1375]*†	<.001
Outcome				
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]				
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

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

	Admission			Day-2			Day 4			*P* Value (group)	*P* Value (time x group)
	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)		
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
IL-6 (pg/mL)	165.7 [39.9-1364.8]	487.1 [201.4-2562.8]*	828.5 [144.9-6098.5]*	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 [126.4-897.1]*	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 [4.5-21.3]*	6.7 [1.9-19.1]*	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 [24.1-114.4]*†	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]	252.6 [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]*†	5.2 [2.7-11.2]	5.4 [3.7-8.0]	9.5 [4.3-23.7]*†	<.001	.36
ANG-2:ANG-1	2.1 [0.6-9.0]	2.4 [0.8-14.5]	8.4 [2.4-30.0]*†	3.7 [1.2-12.3]	7.0 [1.8-20.9]	24.1 [7.9-59.4]*†	2.6 [0.7-9.6]	3.6 [1.8-6.8]	14.7 [4.5-38.6]*†	<.001	.98

eTable 17 continued

	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)		
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 [3.6 - 14.5]	11.8 [6.0 - 16.6]	14.5 [6.6 - 23.1]*	8.4 [4.3 - 18.6]	8.5 [5.0 - 18.8]	13.0 [7.0 - 22.8]*	<.001	.81
Protein C (ng/mL)	112.5 [86.1 - 146.1]	86.2 [74.5 - 121.8]*	110.1 [86.7 - 139.7]†	117.9 [91.4 - 156.0]	92.9 [68.1 - 115.9]*	112.8 [85.4 - 140.7]†	128.9 [101.7 - 169.2]	121.6 [78.7 - 157.5]	110.7 [79.7 - 160.0]*	.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 [393.0 - 960.4]	645.8 [391.9 - 985.4]	545.5 [387.2 - 823.8]	899.7 [534.2 - 1414.0]	936.8 [668.0 - 1676.6]	696.9 [430.2 - 1031.3]*†	.11	.049
PT (sec)	15.3 [12.9 - 17.8]	14.8 [12.6 - 18.8]	17.5 [14.4 - 23.0]*†	15.0 [12.0 - 17.0]	13.0 [11.8 - 16.0]	16.0 [13.0 - 20.0]*†	14.0 [12.0 - 16.0]	12.0 [11.0 - 16.0]	15.0 [12.0 - 17.0]†	<.001	.008
aPTT (sec)	37.0 [29.5 - 52.0]	35.5 [30.5 - 41.2]	47.0 [37.0 - 64.8]*†	39.0 [29.0 - 47.0]	35.5 [30.2 - 38.0]	46.0 [38.0 - 58.8]*†	32.5 [27.2 - 50.5]	27.0 [25.5 - 31.0]	40.0 [33.0 - 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 [102.2 - 247.2]	147.0 [76.0 - 203.0]	111.5 [43.5 - 181.8]*†	172.0 [88.0 - 263.0]	168.0 [80.2 - 218.8]	88.5 [30.0 - 172.5]*†	<.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

eTable 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

	No AKI (n = 91)	AKI		*P* Value
		Transient AKI (n = 25)	Persistent AKI (n = 109)	
Demographics				
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
Immune compromise	22 (24.2)	5 (20.0)	20 (18.3)	.63
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 (29.4)	.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)[a]	10.0 [5.1 - 17.6]	17.5 [6.3 - 34.5]*	19.2 [10.4 - 39.4]*	<.001
Inotropes	7 (7.7)	2 (8.0)	27 (24.8)*	.002
Dose of inotropes (mg)[a]	150.2 [45.0 - 350.6]	180.7 [161.8 - 199.5]	120.8 [54.0 - 259.2]	.93
RRT	0 (0.0)	0 (0.0)	35 (32.1)*†	<.001
Nephrotoxic drugs (≥ one)	55 (60.4)	16 (64.0)*	91 (83.5)*	.001
Aminoglycoside	17 (18.7)	8 (32.0)*	42 (38.5)*	.007
Glycopeptide	18 (19.8)	2 (8.0)	13 (11.9)	.20
Colloid	43 (47.3)	15 (60.0)*	76 (69.7)*	.006
Other [b]	2 (2.2)	1 (4.0)	5 (4.6)	.58
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

eTable 18 continued

	No AKI (n = 91)	AKI		*P* Value
		Transient AKI (n = 25)	Persistent AKI (n = 109)	
Renal function during the first 24 hours				
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
Recurrence of MV	3 (3.3)	3 (12.0)	8 (7.3)	.17
MV-free days[d]	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[d]	90 [50 - 90]	90 [46 - 90]	60 [2 - 90]*†	<.001
Complications[e]				
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[d]	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 $\chi 2$ 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=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)	AKI		*P* Value
		Transient AKI (n = 26)	Persistent AKI (n = 110)	
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 [7 - 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)[a]	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)[a]	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 [b]	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[c]	2 (1.6)	0 (0.0)	3 (2.7)	.80
Unknown	0 (0.0)	0 (0.0)	3 (2.7)	.22

eTable 19 continued

	No AKI (n = 126)	AKI		*P* Value
		Transient AKI (n = 26)	Persistent AKI (n = 110)	
Renal function during the first 24 hours				
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 days[d]	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 days[d]	90 [52 - 90]	90 [30 - 90]	47 [2 - 90]*†	<.001
Complications[e]				
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)*	.001
90-day mortality	40 (31.7)	8 (30.8)	59 (53.6)*	.002
1-year mortality	59 (46.8)	12 (46.2)	69 (62.7)	.036
ICU-free days[d]	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 $\chi 2$ 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=1), Postoperative wound infections (n=3), Upper respiratory tract 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 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

	Admission			Day-2			Day 4			*P* Value (group)	*P* Value (time x group)
	No AKI (n=126)	Transient AKI (n=26)	Persistent AKI (n=110)	No AKI (n=99)	Transient AKI (n=26)	Persistent AKI (n=65)	No AKI (n=52)	Transient AKI (n=15)	Persistent AKI (n=38)		
Inflammatory responses											
IL-10 (pg/mL)	8.7 [4.1 - 27.6]	17.6 [8.6 - 47.4]	55.6 [15.0 - 230.2]*†	4.6 [2.1 - 9.2]	5.4 [3.2 - 9.6]	16.4 [6.0 - 45.0]*†	2.9 [2.0 - 5.4]	5.0 [3.6 - 6.6]	9.6 [4.0 - 30.4]*	<.001	.08
IL-6 (pg/mL)	124.0 [36.6 - 851.6]	434.8 [184.1 - 831.5]	675.6 [139.9 - 4959.0]*	34.7 [16.6 - 133.4]	64.4 [23.2 - 186.9]	106.4 [35.3 - 537.7]*	42.1 [11.4 - 87.7]	44.7 [14.0 - 83.9]	46.3 [17.4 - 113.0]	<.001	.004
IL-8 (pg/mL)	87.7 [29.2 - 243.1]	172.3 [124.7 - 567.6]*	555.2 [129.0 - 2642.5]*	38.6 [20.3 - 80.9]	91.3 [35.9 - 144.0]*	139.6 [75.6 - 684.9]*†	31.4 [17.2 - 131.3]	59.2 [40.4 - 89.7]	111.4 [65.7 - 222.5]*	<.001	.032
MMP-8 (ng/mL)	3.6 [0.6 - 9.2]	7.1 [4.5 - 17.9]*	7.2 [1.8 - 19.9]*	1.8 [0.6 - 4.8]	3.9 [1.0 - 7.2]	2.7 [0.7 - 13.1]	1.0 [0.4 - 2.3]	1.3 [0.6 - 4.1]	2.6 [0.4 - 5.5]	.015	.26
Endothelial cell activation											
Fractalkine (pg/mL)	19.9 [13.2 - 37.2]	33.4 [15.2 - 55.6]	50.0 [22.5 - 110.6]*	15.6 [11.2 - 31.3]	23.8 [12.9 - 79.8]	39.0 [15.4 - 90.6]*	14.2 [11.0 - 27.7]	39.9 [20.2 - 58.2]*	40.4 [23.7 - 83.0]*	<.001	.40
sE-Selectin (ng/mL)	9.5 [3.9 - 21.4]	10.5 [5.6 - 28.7]	13.7 [4.9 - 33.2]	8.9 [4.3 - 16.4]	11.2 [4.7 - 21.3]	9.9 [3.8 - 18.8]	7.6 [4.1 - 15.1]	7.3 [5.1 - 12.0]	9.1 [4.2 - 18.6]	.25	.26
sICAM-1 (ng/mL)	151.8 [83.7 - 318.4]	166.9 [85.2 - 358.1]	242.8 [131.1 - 369.8]*	180.6 [117.7 - 277.4]	183.6 [115.7 - 345.4]	234.1 [135.7 - 427.8]	185.0 [112.7 - 312.8]	194.0 [137.9 - 348.3]	251.0 [196.7 - 396.1]*	.002	.73
Angiopoietin-1 (ng/mL)	2.7 [1.0 - 6.7]	4.1 [1.3 - 9.9]	1.3 [0.6 - 4.6]*†	2.2 [0.9 - 5.2]	1.8 [0.8 - 3.2]	1.0 [0.5 - 1.6]*	3.2 [1.3 - 6.9]	1.6 [1.1 - 3.2]	0.8 [0.4 - 2.6]*	.001	.12
Angiopoietin-2 (ng/mL)	5.9 [2.5 - 11.0]	7.7 [4.1 - 24.1]	12.2 [5.6 - 26.5]*	6.1 [3.1 - 10.7]	7.1 [4.1 - 13.9]	15.2 [7.1 - 38.5]*	4.2 [2.2 - 8.6]	4.9 [3.4 - 7.0]	8.1 [3.7 - 15.3]	.017	.21
ANG-2:ANG-1	2.1 [0.5 - 7.5]	1.9 [0.7 - 11.5]	7.1 [1.4 - 29.7]*†	2.3 [0.7 - 10.5]	5.0 [1.5 - 19.9]	15.0 [6.1 - 40.0]*	1.4 [0.4 - 4.9]	3.4 [1.6 - 5.8]	8.2 [2.5 - 25.4]*	<.001	.83

eTable 20 continued

	Admission			Day-2			Day 4			*P* Value (group)	*P* Value (time x group)
	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=...)		
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 - 177.4]	121.6 [83.8 - 162.5]	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]	702.6 [417.7 - 1008.7]	650.9 [391.9 - 1033.1]	671.6 [422.4 - 1022.2]	962.8 [606.6 - 1433.2]	936.8 [695.3 - 1499.7]	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

eTable 21. Baseline characteristics and outcomes of patients admitted to the ICU with septic shock of short duration (< 52 hours) and with blood genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury

	No AKI (n = 54)	AKI		*P* Value
		Transient AKI (n = 12)	Persistent AKI (n = 46)	
Demographics				
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)	2 (4.3)	.043
Antiplatelet drugs	16 (31.4)	3 (25.0)	16 (35.6)	.84
Severity at time of admission to ICU				
APACHE IV score	80 [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

	No AKI (n = 54)	AKI		*P* Value
		Transient AKI (n = 12)	Persistent AKI (n = 46)	
Renal function during the first 24 hours				
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[d]	86 [60 - 88]	86 [16 - 88]	16 [1 - 87]*	.008
Use of RRT	1 (1.9)	0 (0.0)	14 (30.4)*	<.001
RRT-free days[d]	90 [67 - 90]	90 [25 - 90]	26 [2 - 90]*†	<.001
Complications[e]				
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[d]	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).

[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: 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 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)	AKI		*P* Value
		Transient AKI (n = 16)	Persistent AKI (n = 123)	
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 - 199.5]	225.5 [143.0 - 408.3]	.48
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)*	.008
Other[b]	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
Other[c]	2 (2.4)	1 (6.2)	3 (2.4)	.51
Unknown	0 (0.0)	0 (0.0)	2 (1.6)	.58

eTable 22 continued

	No AKI (n = 83)	AKI		*P* Value
		Transient AKI (n = 16)	Persistent AKI (n = 123)	
Renal function during the first 24 hours				
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[d]	67 [2 - 84]	79 [72 - 83]	29 [1 - 79]*†	.005
Use of RRT	11 (13.3)	0 (0.0)	67 (54.5)*†	<.001
RRT-free days[d]	90 [17 - 90]	90 [90 - 90]	36 [5 - 88]	<.001
Complications[e]				
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[d]	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).

[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=3), Upper respiratory tract infections (n=2), 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 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 [4.1-57.8]	42.2 [23.2-176.4]*	52.9 [14.7-260.1]*†	6.9 [2.9-18.0]	11.6 [7.6-33.7]	20.4 [8.9-88.9]*	5.3 [2.4-13.1]	4.0 [2.7-7.9]	15.1 [5.2-35.2]*†	<0.001	0.020
IL-6 (pg/mL)	475.2 [63.4-2587.9]	2612.9 [212.9-6481.0]	1061.4 [152.1-6271.5]	90.1 [27.9-422.6]	176.2 [63.3-214.2]	276.7 [41.5-1416.7]*	51.7 [12.6-199.4]	21.7 [9.3-26.3]	56.6 [21.1-131.1]†	0.038	0.002
IL-8 (pg/mL)	121.5 [45.2-783.2]	615.6 [162.9-1078.3]	575.1 [132.7-2697.7]*	56.7 [27.1-196.9]	167.0 [93.3-211.5]	314.6 [80.9-1040.5]*	46.0 [16.1-116.0]	55.3 [38.3-76.0]	110.4 [60.6-279.0]*†	<0.001	0.17
MMP-8 (ng/mL)	2.7 [1.0-7.1]	15.0 [6.0-21.8]*	6.5 [2.0-18.0]*	2.1 [0.7-7.2]	6.8 [2.4-17.2]	6.3 [2.0-18.3]*	1.2 [0.6-3.4]	1.4 [0.9-6.8]	4.5 [1.3-10.0]*	<0.001	0.45
Endothelial cell activation											
Fractalkine (pg/mL)	28.2 [16.6-74.0]	34.3 [18.2-61.4]	55.7 [25.7-122.0]*	24.4 [12.9-49.1]	33.5 [23.5-40.5]	69.3 [33.7-142.7]*†	25.4 [14.5-50.8]	26.8 [16.8-44.9]	76.0 [45.1-171.3]*†	<0.001	0.09
sE-Selectin (ng/mL)	10.0 [4.1-24.2]	21.6 [6.2-51.0]	14.7 [6.1-30.5]	11.7 [3.8-22.9]	12.8 [6.5-22.2]	13.2 [5.0-27.2]	7.8 [4.5-21.5]	7.3 [3.8-18.2]	8.2 [4.7-16.1]	0.65	0.048
sICAM-1 (ng/mL)	185.9 [97.1-308.9]	232.9 [109.8-395.8]	221.6 [109.3-356.5]	231.7 [110.4-378.5]	264.0 [144.7-467.6]	277.6 [156.8-400.4]	259.3 [150.1-374.8]	215.7 [83.4-366.1]	271.5 [175.3-426.5]	0.17	0.31
Angiopoietin-1 (ng/mL)	2.2 [0.7-5.7]	3.6 [1.2-8.5]	1.6 [0.7-2.8]	1.6 [0.8-3.7]	1.7 [0.8-4.0]	1.0 [0.6-2.0]*	1.4 [0.7-3.2]	1.6 [0.9-4.4]	0.7 [0.4-1.7]*†	0.004	0.80
Angiopoietin-2 (ng/mL)	6.2 [2.9-13.1]	13.6 [6.7-23.6]	15.3 [5.8-33.7]*	8.6 [4.9-17.4]	20.3 [12.4-25.0]*	19.3 [13.5-55.8]*	6.0 [2.8-13.3]	7.3 [5.2-12.0]	12.3 [5.8-27.2]*	<0.001	0.78
ANG-2:ANG-1	2.2 [0.8-10.3]	2.4 [0.8-15.4]	9.8 [3.5-28.7]*	6.0 [2.0-16.1]	10.0 [4.3-22.9]	28.1 [10.3-66.5]*†	4.4 [1.5-15.0]	5.2 [2.2-11.2]	17.5 [5.2-44.0]*†	<0.001	0.99

eTable 23 continued

	Admission			Day-2			Day 4			*P* Value (group)	*P* Value (time x group)
	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=...)		
Coagulation activation											
D-dimer (µg/mL)	6.9 [4.4-13.6]	9.9 [4.6-15.6]	10.9 [4.9-22.1]	8.3 [3.8-15.2]	14.3 [7.3-17.2]	12.7 [5.8-22.6]*	8.2 [4.8-18.7]	16.6 [11.0-20.1]	12.8 [6.9-22.6]*	0.013	0.65
Protein C (ng/mL)	110.0 [88.1-143.2]	86.5 [77.6-117.6]	109.3 [87.8-138.0]	115.9 [85.1-138.4]	88.1 [65.6-115.0]	110.9 [81.6-129.7]	130.0 [105.7 - 164.1]	109.9 [76.7 - 144.8]	109.5 [80.0 - 145.5]*	0.011	0.32
Antithrombin (ng/mL)	654.7 [394.2-956.1]	611.4 [376.8-1155.2]	574.5 [392.5-909.1]	614.9 [371.0-893.4]	645.8 [390.8-895.4]	495.9 [365.1-732.8]	895.0 [468.2-1374.2]	944.3 [644.0-1728.0]	673.0 [406.7-926.1]*†	0.20	0.036
PT (sec)	15.5 [13.8-18.8]	17.6 [13.2-20.2]	17.9 [14.5-24.7]*	15.0 [13.0-17.0]	14.0 [12.2-16.8]	17.0 [14.0-20.0]*†	14.5 [13.0-16.2]	14.0 [11.0-16.0]	15.0 [12.0-17.0]	0.021	0.009
aPTT (sec)	43.5 [32.8-53.0]	37.0 [32.0-45.0]	47.0 [38.0-68.0]*	39.0 [33.0-44.0]	38.0 [33.0-39.0]	48.0 [40.0-59.5]*†	35.0 [30.0-53.5]	27.0 [25.5-28.2]	42.5 [34.0-53.0]†	<0.001	0.35
Platelets (10^9/L)	139.0 [94.0-223.5]	159.5 [117.2-213.2]	115.0 [60.0-192.0]*	129.0 [74.0-236.0]	136.5 [71.8-181.0]	116.0 [45.0-168.0]*	141.0 [74.5-225.5]	120.0 [78.5-182.0]	88.0 [33.0-151.5]*	0.004	0.31

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

	No AKI (n = 37)	AKI		*P* Value
		Transient AKI (n = 13)	Persistent AKI (n = 63)	
Demographics				
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 - 38.9]*	19.5 [12.5 - 39.2]*	.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 - 199.5]	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 [b]	2 (5.4)	0 (0.0)	3 (4.8)	>.99
Source of infection				
Pulmonary tract	24 (64.9)	5 (38.5)	23 (36.5)*	.018
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

eTable 24 continued

	No AKI (n = 37)	AKI		*P* Value
		Transient AKI (n = 13)	Persistent AKI (n = 63)	
Renal function during the first 24 hours				
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[d]	90 [13 - 90]	90 [87 - 90]	63 [4 - 90]*†	.001
Complications[e]				
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 $\chi 2$ 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=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 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)	AKI		*P* Value
		Transient AKI (n = 46)	Persistent AKI (n = 361)	
Demographics				
Age, years	62 [48 - 71]	57 [47 - 71]	65 [54 - 73]*†	<.001
Male sex	606 (62.6)	29 (63.0)	208 (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]*	.002
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 (11.6)	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 - 254.7	82.9 [48.8 - 218.3]	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 [b]	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
Other[c]	78 (8.1)	2 (4.3)	16 (4.4)	.05
Unknown	3 (0.3)	0 (0.0)	9 (2.5)*	.002

eTable 25 continued

	No AKI (n = 968)	AKI		*P* Value
		Transient AKI (n = 46)	Persistent AKI (n = 361)	
Renal function during the first 24 hours				
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[d]	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[d]	90 [59 - 90]	90 [39 - 90]	34 [3 - 90]*†	<.001
Complications[e]				
None	870 (89.9)	40 (87.0)	306 (84.8)*	.031
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
Hospital length of stay, days	16 [8 - 29]	21 [10 - 38]	14 [4 - 32]*†	.012
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[d]	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 $\chi 2$ 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=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.

[e] Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.

eTable 26. 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 (RIFLE I and F only)

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 26)	Persistent AKI (n = 238)	
Demographics				
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 (88.5)	.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)	10 (4.2)	.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 (68.1)*†	<.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
Other [b]	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
Other[c]	19 (3.8)	0 (0.0)	8 (3.4)	.87
Unknown	0 (0.0)	0 (0.0)	5 (2.1)*	.007

eTable 26 continued

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 26)	Persistent AKI (n = 238)	
Renal function during the first 24 hours				
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[d]	84 [29 - 88]	85 [67 - 88]	23 [2 - 84]*†	<.001
Use of RRT	18 (3.6)	3 (11.5)	108 (45.4)*†	<.001
RRT-free days[d]	90 [44 - 90]	90 [89 - 90]	39 [3 - 90]*†	<.001
Complications[e]				
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[d]	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 $\chi 2$ 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=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 [3.0-21.1]	26.1 [13.6-51.5]*	52.2 [14.0-246.7]*	4.3 [2.0-10.0]	7.8 [3.7-14.4]	21.0 [8.1-81.8]*†	3.5 [1.8-8.0]	4.4 [2.8-5.5]	15.1 [5.4-35.6]*†	<0.001	<0.001
IL-6 (pg/mL)	102.0 [27.1-474.5]	255.0 [48.3-780.1]	586.5 [96.5-5739.9]*†	44.2 [15.1-149.5]	124.5 [42.8-198.0]*	129.2 [40.2-966.2]*	27.0 [10.7-108.1]	25.6 [11.2-55.7]	59.3 [22.4-139.0]*†	<0.001	<0.001
IL-8 (pg/mL)	61.5 [24.2-182.7]	205.5 [45.5-435.5]*	431.0 [110.2-2339.4]*†	32.6 [15.9-87.9]	124.1 [54.4-184.3]*	185.4 [70.3-760.8]*	29.2 [13.8-86.1]	64.4 [38.6-136.1]	116.1 [62.9-273.3]*	<0.001	0.001
MMP-8 (ng/mL)	2.0 [0.6-5.8]	7.1 [2.5-14.6]*	6.4 [1.8-19.8]*	1.5 [0.5-3.9]	2.8 [1.1-5.5]*	4.5 [1.2-15.5]*	1.0 [0.4-2.1]	1.3 [0.5-1.7]	3.1 [0.8-8.5]*	<0.001	0.31
Endothelial cell activation											
Fractalkine (pg/mL)	19.9 [12.8-38.8]	21.7 [13.9-49.5]	52.7 [23.7-115.3]*†	16.7 [12.8-34.1]	20.2 [11.3-54.8]	55.7 [25.9-127.8]*†	18.4 [12.8-44.9]	33.3 [15.0-49.9]	59.0 [32.6-142.0]*†	<0.001	0.022
sE-Selectin (ng/mL)	8.8 [4.2-21.2]	11.9 [5.3-26.0]	14.3 [5.9-34.7]*	8.9 [4.0-17.3]	8.6 [4.7-20.8]	12.1 [4.7-24.7]*	7.6 [3.6-15.1]	5.3 [4.1-14.6]	9.7 [4.7-19.0]	<0.001	0.017
sICAM-1 (ng/mL)	155.7 [88.2-286.5]	161.2 [105.7-234.6]	230.4 [140.4-395.6]*	169.4 [105.3-300.3]	147.2 [109.8-292.0]	276.9 [148.7-458.2]*†	203.6 [109.8-335.5]	163.1 [105.5-254.6]	275.8 [175.3-430.6]*†	<0.001	0.28
Angiopoietin-1 (ng/mL)	2.6 [1.0-6.2]	3.6 [1.3-7.2]	1.4 [0.7-3.7]*†	2.0 [0.9-5.3]	2.2 [0.8-3.2]	1.0 [0.6-1.9]*†	2.1 [0.9-4.7]	1.8 [1.0-2.3]	0.8 [0.5-2.3]*	<0.001	0.026
Angiopoietin-2 (ng/mL)	4.7 [2.2-9.3]	7.0 [3.2-15.7]	13.6 [6.0-30.4]*†	5.5 [2.6-10.3]	7.1 [3.8-13.1]	18.5 [9.3-44.5]*†	4.0 [2.0-9.4]	4.6 [3.1-7.8]	9.6 [4.7-25.1]*	<0.001	0.28
ANG-2:ANG-1	1.7 [0.5-6.1]	2.2 [0.6-5.5]	9.6 [2.5-30.8]*†	2.3 [0.6-9.2]	4.9 [2.1-13.8]	22.4 [6.6-56.6]*†	1.7 [0.5-7.6]	3.6 [2.7-5.9]	14.5 [4.2-37.1]*†	<0.001	0.99

eTable 27 continued

	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)		
Coagulation activation											
D-dimer (µg/mL)	7.3 [3.3-15.4]	7.2 [2.1-14.1]	12.1 [5.6-23.8]*†	6.3 [3.3-12.7]	9.3 [4.6-14.6]	14.4 [6.7-25.1]*†	8.3 [4.5-16.0]	6.9 [2.8-19.2]	13.6 [7.1-24.2]*†	<0.001	0.66
Protein C (ng/mL)	122.7 [90.0-159.0]	110.8 [77.9-157.6]	111.1 [86.1-142.6]	125.3 [94.8-169.1]	107.9 [67.5-126.0]*	112.2 [83.6-140.1]*	141.3 [100.8 - 198.7]	129.9 [122.3 - 141.7]	107.0 [79.5 - 150.8]*	<0.001	0.019
Antithrombin (ng/mL)	773.7 [539.5-1111.2]	621.0 [494.0-977.4]	615.3 [394.5-929.9]*	778.7 [490.9-1130.6]	780.6 [515.9-1033.7]	568.8 [399.6-894.1]*	934.4 [585.7-1446.2]	1070.6 [831.8-1808.3]	723.1 [467.6-1144.7]*†	<0.001	0.038
PT (sec)	14.8 [12.5-17.3]	13.6 [12.6-16.6]	17.4 [14.2-22.8]*†	14.0 [12.0-16.0]	13.0 [12.0-14.8]	16.0 [13.0-19.8]*†	14.0 [12.0-15.0]	12.0 [11.0-14.0]	14.0 [12.0-17.0]*†	<0.001	<0.001
aPTT (sec)	34.0 [29.0-44.0]	37.5 [29.8-48.8]	45.0 [36.0-64.0]*†	33.0 [29.0-43.0]	36.0 [33.5-38.0]	46.0 [36.0-59.0]*†	30.0 [26.0-45.8]	27.0 [27.0-35.0]	40.0 [33.0-49.0]*	<0.001	0.07
Platelets (10^9/L)	181.5 [123.0-261.2]	158.5 [98.0-246.0]	111.5 [45.2-195.8]*†	182.0 [112.0-265.0]	141.5 [90.8-223.0]	116.0 [44.5-179.5]*	196.0 [116.5-274.5]	159.5 [87.5-179.0]	85.0 [31.2-174.0]*	<0.001	0.004

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 28. 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)	AKI		*P* Value
		Transient AKI (n = 11)	Persistent AKI (n = 102)	
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 (82.5)	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 compromise	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]	.58
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
Beta-adrenergic 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 antidiabetic drugs	20 (8.9)	1 (9.1)	16 (15.7)	.18
Corticosteroids	31 (13.8)	1 (9.1)	6 (5.9)	.08
Antiplatelet 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)[a]	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)[a]	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 [b]	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[c]	2 (0.9)	0 (0.0)	0 (0.0)	>.99
Unknown	225 (100.0)	11 (100.0)	102 (100.0)	>.99

eTable 28 continued

	No AKI (n = 225)	AKI		*P* Value
		Transient AKI (n = 11)	Persistent AKI (n = 102)	
Renal function during the first 24 hours				
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				
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[d]	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[d]	90 [55 - 90]	90 [90 - 90]	24 [2 - 90]	<.001
Complications[e]				
None	199 (88.4)	9 (81.8)	79 (77.5)*	.033
ICU-acquired AKI	17 (7.6)	0 (0.0)	9 (8.8)	.73
ICU-acquired ARDS	3 (1.3)	1 (9.1)	3 (2.9)	.12
ICU-acquired infection	13 (5.8)	1 (9.1)	17 (16.7)*	.007
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
1-year mortality	91 (40.4)	3 (27.3)	63 (61.8)*	.001
ICU-free days[d]	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).

[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: Oral infections (n=1), Postoperative wound infections (n=1)

[c] Between inclusion and day-90.

[e] 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

	No AKI (n = 968)	AKI		*P* Value
		Transient AKI (n = 151)	Persistent AKI (n = 426)	
Demographics				
Age, years	62 [48 - 71]	64 [51 - 73]	65 [54 - 73]*	<.001
Male sex	606 (62.6)	87 (57.6)	249 (58.5)	.23
Race, white	847 (88.0)	133 (88.1)	376 (89.7)	.65
Medical admission	721 (74.5)	111 (73.5)	305 (71.6)	.52
Chronic comorbidities				
None	318 (32.9)	40 (26.5)	126 (29.6)	.20
Cardiovascular compromise	229 (23.7)	51 (33.8)*	110 (25.8)	.031
Hypertension	229 (23.7)	49 (32.5)	120 (28.2)	.029
Diabetes	159 (16.4)	35 (23.2)	77 (18.1)	.12
Liver cirrhosis	13 (1.3)	4 (2.6)	15 (3.5)*	.024
Immune compromise	184 (19.0)	29 (19.2)	83 (19.5)	.98
Malignancy	200 (20.7)	32 (21.2)	102 (23.9)	.39
Charlson comorbidity index	3 [1 - 5]	3 [2 - 5]*	3 [2 - 5]*	<.001
Chronic medication				
Diuretics	185 (19.1)	39 (25.8)	107 (25.1)*	.016
ACE inhibitors / ARBs	223 (23.0)	38 (25.2)	114 (26.8)	.31
Calcium-entry blockers	122 (12.6)	26 (17.2)	60 (14.1)	.26
Beta-adrenergic blockers	222 (22.9)	43 (28.5)	120 (28.2)	.06
NSAIDs and Cox II inhibitors	112 (11.6)	17 (11.3)	48 (11.3)	.99
Oral antidiabetic drugs	113 (11.7)	29 (19.2)*	53 (12.4)	.041
Corticosteroids	99 (10.2)	15 (9.9)	41 (9.6)	.96
Antiplatelet drugs	208 (22.5)	39 (26.5)	97 (23.5)	.54
Severity at time of admission to ICU				
APACHE IV score	67 [52 - 85]	79 [67 - 99]*	96 [75 - 121]*†	<.001
Acute physiology score	55 [42 - 71]	67 [55 - 85]*	82 [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)	103 (68.2)*	319 (74.9)*	<.001
ARDS	192 (19.8)	40 (26.5)	125 (29.3)*	<.001
Therapy during the first 24h				
Mechanical ventilation	773 (79.9)	129 (85.4)	356 (83.6)	.11
Vasopressors	503 (52.0)	120 (79.5)*	356 (83.6)*	<.001
Dose of vasopressors (mg)[a]	5.8 [2.0 - 13.3]	12.0 [5.0 - 21.6]*	15.8 [5.7 - 34.5]*	<.001
Inotropes	40 (4.1)	19 (12.6)*	73 (17.1)*	<.001
Dose of inotropes (mg)[a]	151.3 [46.7 - 254.7]	143.0 [66.0 - 279.1]	192.3 [62.9 - 315.0]	.49
RRT	6 (0.6)	6 (4.0)*	95 (22.4)*†	<.001
Nephrotoxic drugs (≥ one)	379 (39.2)	74 (49.0)	263 (61.7)*†	<.001
Aminoglycoside	128 (13.2)	30 (19.9)	123 (28.9)*	<.001
Glycopeptide	106 (11.0)	18 (11.9)	72 (16.9)*	.010
Colloid	163 (16.8)	38 (25.2)*	167 (39.2)*†	<.001
Other[b]	94 (9.7)	15 (9.9)	32 (7.5)	.40
Source of infection				
Pulmonary tract	562 (58.1)	75 (49.7)	143 (33.6)*†	<.001
Abdominal	134 (13.8)	38 (25.2)*	118 (27.7)*	<.001
Cardiovascular	70 (7.2)	12 (7.9)	58 (13.6)*	.001
Urinary tract	43 (4.4)	8 (5.3)	42 (9.9)*	.001
CNS	56 (5.8)	6 (4.0)	9 (2.1)*	.007
Skin or soft tissue	22 (2.3)	5 (3.3)	25 (5.9)*	.003
Other[c]	78 (8.1)	7 (4.6)	19 (4.5)*	.027
Unknown	3 (0.3)	0 (0.0)	12 (2.8)*	<.001

eTable 29 continued

	No AKI	AKI	*P* Value

	(n = 968)	Transient AKI (n = 151)	Persistent AKI (n = 426)	
Renal function during the first 24 hours				
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				
Duration of initial MV, days	2 [1 - 5]	3 [2 - 8]*	2 [1 - 7]*†	<.001
Recurrence of MV	24 (2.5)	11 (7.3)*	22 (5.2)*	.002
MV-free days[d]	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[d]	90 [59 - 90]	90 [43 - 90]*	38 [3 - 90]*†	<.001
Complications[e]				
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	365 (37.7)	61 (40.4)	257 (60.3)*†	<.001
ICU-free days[d]	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.

eTable 30. 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 96-hour cutoff

	No AKI (n = 968)	AKI		*P* Value
		Transient AKI (n = 167)	Persistent AKI (n = 410)	
Demographics				
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	55 [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)[a]	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)[a]	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
Nephrotoxic 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)*	.009
Colloid	163 (16.8)	47 (28.1)*	158 (38.5)*	<.001
Other[b]	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[c]	78 (8.1)	7 (4.2)	19 (4.6)	.027
Unknown	3 (0.3)	0 (0.0)	12 (2.9)*	<.001

eTable 30 continued

	No AKI (n = 968)	AKI		*P* Value
		Transient AKI (n = 167)	Persistent AKI (n = 410)	
Renal function during the first 24 hours				
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]*	13.6 [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				
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[d]	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[d]	90 [59 - 90]	90 [40 - 90]	37 [3 - 90]*†	<.001
Complications[e]				
None	870 (89.9)	142 (85.0)	353 (86.1)	.048
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[d]	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).

[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.

eTable 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

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 97)	Persistent AKI (n = 272)	
Demographics				
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 [65 - 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)[a]	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)[a]	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[b]	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[c]	19 (3.8)	3 (3.1)	8 (2.9)	.89
Unknown	0 (0.0)	0 (0.0)	6 (2.2)*	.004

eTable 31 continued

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 97)	Persistent AKI (n = 272)	
Renal function during the first 24 hours				
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				
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[d]	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[d]	90 [44 - 90]	90 [51 - 90]	40 [3 - 90]*†	<.001
Complications[e]				
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)	138 (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[d]	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 $\chi 2$ 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.

eTable 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

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 111)	Persistent AKI (n = 258)	
Demographics				
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 compromise	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)	3 (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)*	.018
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 (86.8)*	<.001
Dose of vasopressors (mg)[a]	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)[a]	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[b]	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

	No AKI (n = 497)	AKI		*P* Value
		Transient AKI (n = 111)	Persistent AKI (n = 258)	
Renal function during the first 24 hours				
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[d]	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[d]	90 [44 - 90]	90 [43 - 90]	37 [3 - 90]*†	<.001
Complications[e]				
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)	.58
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[d]	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 $\chi 2$ 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.

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= 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)		
Inflammatory responses											
IL-10 (pg/mL)	7.2 [3.0-21.1]	18.8 [8.4-53.1]*	45.3 [12.5-193.6]*†	4.3 [2.0-10.0]	7.5 [3.4-16.5]*	18.1 [7.7-65.4]*†	3.5 [1.8-8.0]	4.6 [2.5-10.1]	14.2 [5.3-36.2]*†	<0.001	<0.001
IL-6 (pg/mL)	102.0 [27.1-474.5]	331.0 [74.4-1464.3]*	511.9 [91.7-4553.5]*	44.2 [15.1-149.5]	66.7 [28.6-190.4]*	133.4 [35.6-853.3]*†	27.0 [10.7-108.1]	31.5 [11.2-71.5]	62.6 [20.1-139.8]*†	<0.001	<0.001
IL-8 (pg/mL)	61.5 [24.2-182.7]	169.7 [78.7-570.6]*	363.1 [102.5-2080.6]*†	32.6 [15.9-87.9]	96.2 [36.3-179.3]*	173.0 [69.0-696.6]*†	29.2 [13.8-86.1]	59.2 [31.6-130.6]*	110.1 [61.2-277.6]*†	<0.001	<0.001
MMP-8 (ng/mL)	2.0 [0.6-5.8]	7.0 [2.0-16.9]*	6.1 [1.8-15.9]*	1.5 [0.5-3.9]	3.0 [1.2-9.4]*	4.0 [1.2-14.3]*	1.0 [0.4-2.1]	1.6 [0.7-3.7]*	2.8 [0.8-7.8]*	<0.001	0.18
Endothelial cell activation											
Fractalkine (pg/mL)	19.9 [12.8-38.8]	30.2 [15.0-64.2]*	49.4 [22.8-109.3]*†	16.7 [12.8-34.1]	27.2 [13.4-56.4]*	51.4 [23.5-125.4]*†	18.4 [12.8-44.9]	27.3 [15.9-53.3]	63.2 [33.6-141.1]*†	<0.001	0.005
sE-Selectin (ng/mL)	8.8 [4.2-21.2]	12.1 [5.4-33.1]*	13.1 [5.5-30.2]*	8.9 [4.0-17.3]	11.1 [4.7-24.6]	11.4 [4.1-22.4]	7.6 [3.6-15.1]	9.7 [4.2-17.3]	8.7 [4.5-18.0]	0.001	0.015
sICAM-1 (ng/mL)	155.7 [88.2-286.5]	185.2 [105.6-334.4]	223.6 [133.0-388.2]*	169.4 [105.3-300.3]	195.1 [121.6-330.8]	269.2 [138.7-435.6]*	203.6 [109.8-335.5]	219.5 [129.4-353.6]	271.1 [177.9-419.1]*	<0.001	0.77
Angiopoietin-1 (ng/mL)	2.6 [1.0-6.2]	3.1 [1.1-7.8]	1.5 [0.7-3.4]*†	2.0 [0.9-5.3]	2.0 [0.9-3.2]	1.0 [0.6-1.9]*†	2.1 [0.9-4.7]	1.7 [0.7-4.0]	0.8 [0.4-2.1]*†	<0.001	0.015
Angiopoietin-2 (ng/mL)	4.7 [2.2-9.3]	8.8 [3.9-19.6]*	12.0 [5.5-26.0]*†	5.5 [2.6-10.3]	8.6 [4.0-19.9]*	16.8 [9.3-43.2]*†	4.0 [2.0-9.4]	5.6 [3.7-10.8]	9.5 [4.7-23.1]*†	<0.001	0.22
ANG-2:ANG-1	1.7 [0.5-6.1]	2.4 [0.7-13.1]	8.2 [2.3-26.2]*†	2.3 [0.6-9.2]	5.0 [1.7-17.3]*	20.0 [6.9-55.1]*†	1.7 [0.5-7.6]	3.6 [1.1-9.4]	14.6 [4.6-36.6]*†	<0.001	0.99

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 [94.8-169.1]	103.4 [74.9-139.7]*	114.7 [84.9-144.2]*	141.3 [100.8 - 198.7]	130.7 [84.6 - 163.1]	107.0 [76.4 - 150.8]*	<0.001	0.033
Antithrombin (ng/mL)	773.7 [539.5-1111.2]	659.8 [423.5-981.6]*	641.1 [402.0-964.1]*	778.7 [490.9-1130.6]	601.8 [395.0-953.1]*	603.3 [409.0-904.9]*	934.4 [585.7-1446.2]	779.7 [611.2-1268.9]	718.2 [459.6-1169.9]*	<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 [12.0-16.0]	14.0 [12.0-17.0]	15.0 [13.0-19.0]*†	14.0 [12.0-15.0]	14.0 [11.0-15.0]	14.0 [12.0-17.0]	<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 [29.0-43.0]	36.0 [31.0-40.2]	44.0 [35.0-54.8]*†	30.0 [26.0-45.8]	36.0 [27.0-46.8]	39.0 [32.0-48.0]*	<0.001	0.09
Platelets (10^9/L)	181.5 [123.0-261.2]	193.0 [113.0-254.0]	115.5 [46.0-197.5]*†	182.0 [112.0-265.0]	167.0 [94.5-228.0]	111.0 [44.8-178.0]*†	196.0 [116.5-274.5]	156.0 [80.5-202.5]	73.5 [30.0-171.2]*†	<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

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

	Admission			Day-2			Day 4			*P* Value (group)	*P* Value (time x group)
	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)		
Inflammatory responses											
IL-10 (pg/mL)	7.2 [3.0-21.1]	20.4 [8.8-63.0]*	45.8 [12.8-198.3]*†	4.3 [2.0-10.0]	7.7 [3.6-18.7]*	20.0 [7.9-67.5]*†	3.5 [1.8-8.0]	5.6 [2.8-10.6]*	15.5 [4.8-40.8]*†	<0.001	<0.001
IL-6 (pg/mL)	102.0 [27.1-474.5]	337.3 [73.8-1566.1]*	511.9 [92.7-4729.3]*	44.2 [15.1-149.5]	69.8 [29.1-194.8]*	141.1 [35.8-973.8]*†	27.0 [10.7-108.1]	32.7 [12.4-74.8]	62.8 [20.1-173.8]*†	<0.001	<0.001
IL-8 (pg/mL)	61.5 [24.2-182.7]	175.5 [79.5-628.5]*	372.2 [104.7-2123.8]*†	32.6 [15.9-87.9]	105.8 [38.9-186.2]*	192.3 [69.5-753.5]*†	29.2 [13.8-86.1]	59.2 [32.2-115.0]*	112.3 [62.6-309.0]*†	<0.001	<0.001
MMP-8 (ng/mL)	2.0 [0.6-5.8]	6.4 [1.9-16.6]*	6.2 [1.8-16.0]*	1.5 [0.5-3.9]	3.0 [1.2-9.4]*	4.1 [1.2-15.0]*	1.0 [0.4-2.1]	1.7 [0.7-3.9]*	2.8 [0.8-8.4]*	<0.001	0.38
Endothelial cell activation											
Fractalkine (pg/mL)	19.9 [12.8-38.8]	35.2 [15.2-67.7]*	49.2 [22.8-111.9]*†	16.7 [12.8-34.1]	29.9 [13.4-57.3]*	52.2 [23.0-127.9]*†	18.4 [12.8-44.9]	33.1 [16.7-56.9]*	63.9 [34.0-145.3]*†	<0.001	0.003
sE-Selectin (ng/mL)	8.8 [4.2-21.2]	12.0 [5.4-33.2]*	13.1 [5.5-30.2]*	8.9 [4.0-17.3]	11.1 [4.8-22.4]	12.2 [4.0-23.1]	7.6 [3.6-15.1]	8.9 [4.6-16.0]	8.9 [4.1-18.7]	0.001	0.019
sICAM-1 (ng/mL)	155.7 [88.2-286.5]	190.5 [105.5-333.9]	229.1 [133.4-395.6]*	169.4 [105.3-300.3]	183.7 [120.0-325.8]	273.1 [141.1-450.7]*†	203.6 [109.8-335.5]	204.1 [123.4-353.6]	281.3 [191.1-421.6]*†	<0.001	0.58
Angiopoietin-1 (ng/mL)	2.6 [1.0-6.2]	2.7 [1.1-6.8]	1.5 [0.7-3.6]*†	2.0 [0.9-5.3]	1.9 [0.9-3.2]	1.0 [0.5-1.8]*†	2.1 [0.9-4.7]	1.6 [0.7-3.9]	0.8 [0.4-2.1]*†	<0.001	0.016
Angiopoietin-2 (ng/mL)	4.7 [2.2-9.3]	8.8 [4.1-22.4]*	12.1 [5.4-25.5]*†	5.5 [2.6-10.3]	10.0 [4.4-21.9]*	16.8 [8.3-44.0]*†	4.0 [2.0-9.4]	6.4 [3.9-12.4]*	9.5 [4.4-23.1]*	<0.001	0.22
ANG-2:ANG-1	1.7 [0.5-6.1]	2.6 [0.8-16.2]*	8.0 [2.3-26.9]*†	2.3 [0.6-9.2]	6.2 [1.9-19.0]*	20.4 [7.0-57.0]*†	1.7 [0.5-7.6]	4.3 [1.6-10.7]*	14.6 [4.6-36.6]*†	<0.001	0.99

eTable 34 continued

	Admission			Day-2			Day 4			*P* Value (group)	*P* Value (time x group)
	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)		
Coagulation activation											
D-dimer (µg/mL)	7.3 [3.3-15.4]	8.9 [3.9-19.0]	11.9 [6.0-22.4]*†	6.3 [3.3-12.7]	10.6 [4.6-17.9]*	13.7 [6.3-24.6]*†	8.3 [4.5-16.0]	9.4 [4.9-18.8]	13.1 [6.9-22.9]*†	<0.001	0.93
Protein C (ng/mL)	122.7 [90.0-159.0]	103.6 [78.1-150.8]*	111.3 [88.0-143.8]	125.3 [94.8-169.1]	103.0 [73.9-139.8]*	115.4 [87.6-144.1]*	141.3 [100.8 - 198.7]	128.8 [83.2 - 162.5]*	108.2 [79.5 - 150.8]*	<0.001	0.052
Antithrombin (ng/mL)	773.7 [539.5-1111.2]	646.5 [411.5-996.5]*	641.1 [401.7-953.6]*	778.7 [490.9-1130.6]	601.1 [387.2-941.0]*	607.4 [418.8-914.6]*	934.4 [585.7-1446.2]	762.6 [503.2-1216.5]	743.9 [469.4-1195.3]*	<0.001	0.24
PT (sec)	14.8 [12.5-17.3]	15.6 [12.9-18.7]*	17.0 [13.8-22.4]*†	14.0 [12.0-16.0]	14.0 [13.0-18.0]	15.0 [13.0-19.5]*†	14.0 [12.0-15.0]	14.0 [12.0-15.8]	14.0 [12.0-17.0]	<0.001	<0.001
aPTT (sec)	34.0 [29.0-44.0]	37.5 [32.0-47.2]*	45.0 [35.0-64.0]*†	33.0 [29.0-43.0]	36.5 [31.8-43.0]	45.0 [35.0-55.0]*†	30.0 [26.0-45.8]	32.0 [28.5-45.0]	39.0 [33.0-48.8]*	<0.001	0.06
Platelets (10^9/L)	181.5 [123.0-261.2]	189.0 [106.0-252.5]	116.0 [46.5-198.5]*†	182.0 [112.0-265.0]	160.0 [90.0-226.0]*	111.0 [44.2-177.8]*†	196.0 [116.5-274.5]	150.0 [77.8-203.2]*	72.0 [30.0-163.0]*†	<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

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

	No AKI (n = 225)	AKI		*P* Value
		Transient AKI (n = 45)	Persistent AKI (n = 122)	
Demographics				
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				
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
Liver cirrhosis	4 (1.8)	0 (0.0)	3 (2.5)	.74
Immune compromise	51 (22.7)	9 (20.0)	22 (18.0)	.60
Malignancy	50 (22.2)	9 (20.0)	22 (18.0)	.65
Charlson comorbidity index	3 [1 - 5]	3 [2 - 5]	3 [2 - 4]	.77
Chronic medication				
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
NSAIDs and Cox II inhibitors	34 (15.1)	10 (22.2)	11 (9.0)	.07
Oral antidiabetic drugs	20 (8.9)	9 (20.0)	20 (16.4)	.03
Corticosteroids	31 (13.8)	4 (8.9)	7 (5.7)	.06
Antiplatelet drugs	46 (22.9)	11 (25.0)	34 (28.6)	.51
Severity at time of admission to ICU				
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
Shock	91 (40.4)	31 (68.9)*	103 (84.4)*	<.001
ARDS	63 (28.0)	14 (31.1)	47 (38.5)	.14
Therapy during the first 24h				
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)[a]	5.9 [2.3 - 14.4]	16.2 [4.6 - 33.2]*	18.6 [8.8 - 38.5]*	<.001
Inotropes	9 (4.0)	6 (13.3)	25 (20.5)*	<.001
Dose of inotropes (mg)[a]	150.2 [75.5 - 344.8]	145.1 [126.3 - 200.5]	96.9 [53.7 - 264.0]	.91
RRT	0 (0.0)	2 (4.4)	34 (27.9)*†	<.001
Nephrotoxic drugs (≥ one)	115 (51.1)	26 (57.8)	99 (81.1)*†	<.001
Aminoglycoside	44 (19.6)	12 (26.7)	46 (37.7)*	.001
Glycopeptide	25 (11.1)	5 (11.1)	13 (10.7)	>.99
Colloid	72 (32.0)	20 (44.4)	79 (64.8)*	<.001
Other[b]	11 (4.9)	3 (6.7)	7 (5.7)	.81
Source of infection				
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
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[c]	2 (0.9)	2 (4.4)	0 (0.0)	.06
Unknown	0 (0.0)	0 (0.0)	1 (0.8)	.43

eTable 35 continued

	No AKI (n = 225)	AKI		*P* Value
		Transient AKI (n = 45)	Persistent AKI (n = 122)	
Renal function during the first 24 hours				
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				
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 days[d]	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 days[d]	90 [55 - 90]	90 [46 - 90]	28 [3 - 90]*†	<.001
Complications[e]				
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)*	.020
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 days[d]	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).

[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 36. 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

	No AKI (n = 225)	AKI		*P* Value
		Transient AKI (n = 52)	Persistent AKI (n = 115)	
Demographics				
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				
None	74 (32.9)	16 (30.8)	41 (35.7)	.80
Cardiovascular compromise	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	3 [1 - 5]	3 [2 - 5]	3 [2 - 4]	.80
Chronic medication				
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-adrenergic 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
Corticosteroids	31 (13.8)	4 (7.7)	7 (6.1)	.08
Antiplatelet drugs	46 (22.9)	12 (24.0)	33 (29.2)	.46
Severity at time of admission to ICU				
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 (28.0)	16 (30.8)	45 (39.1)	.12
Therapy during the first 24h				
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)[a]	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)[a]	150.2 [75.5 - 344.8]	143.0 [108.8 - 182.8]	102.5 [51.5 - 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[b]	11 (4.9)	3 (5.8)	7 (6.1)	.81
Source of infection				
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[c]	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)	AKI		*P* Value
		Transient AKI (n = 52)	Persistent AKI (n = 115)	
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[d]	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[d]	90 [55 - 90]	90 [38 - 90]	26 [3 - 90]*†	<.001
Complications[e]				
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 (47.8)*†	<.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[d]	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).

[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 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)	AKI		*P* Value
		Transient AKI (n = 39)	Persistent AKI (n = 145)	
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)[a]	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)[a]	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[b]	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

Table 37 continued

	No AKI (n = 448)	AKI		*P* Value
		Transient AKI (n = 39)	Persistent AKI (n = 145)	
Outcome				
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[c]	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[c]	90 [90 - 90]	90 [12 - 90]*	46 [4 - 90]*†	<.001
Complications[d]				
None	386 (86.2)	35 (89.7)	108 (74.5)	.004
ICU-acquired AKI	14 (3.1)	1 (2.6)	6 (4.1)	.85
ICU-acquired ARDS	16 (3.6)	1 (2.6)	11 (7.6)	.11
ICU-acquired infection	46 (10.3)	2 (5.1)	30 (20.7)	.002
ICU length of stay, days	4 [2 - 7]	5 [4 - 8]*	5 [3 - 12]*†	.001
Hospital length of stay, days	14 [7 - 25]	14 [8 - 23]	15 [5 - 29]	.96
ICU-mortality	53 (11.8)	9 (23.1)*	50 (34.5)*	<.001
30-day mortality	92 (20.5)	16 (41.0)*	62 (42.8)*	<.001
60-day mortality	105 (23.4)	17 (43.6)*	74 (51.0)*	<.001
90-day mortality	108 (24.1)	18 (46.2)*	74 (51.0)*	<.001
1-year mortality	141 (31.5)	19 (48.7)*	84 (57.9)*	<.001
ICU-free days[c]	84 [51 - 87]	69 [2 - 83]*	28 [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 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.

[c] Between inclusion and day-90.

[c] Complications were defined as ICU-acquired when diagnosed more than 48h after admission to the ICU.

eTable 38. Admission diagnoses of patients admitted to the ICU for a non-infectious condition and with plasma biomarkers measured upon admission

Medical diagnoses	*N*
Cardiovascular diagnoses	**170**
Cardiac arrest	103
Acute myocardial infarction	21
Congestive heart failure	11
Cardiogenic shock	10
Rhythm disturbance	9
Cardiomyopathy	5
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
Neuromuscular -medical	4
Seizures	2
Medical, other	**34**
Overdose	6
GI Bleeding	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	1
Embolectomy	1
Musculoskeletal -medical, other	1

Surgical diagnoses	*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	*N*
Trauma	**71**
Multiple trauma	44
Head/face trauma	15
Trauma, other	7
Chest/thorax trauma	3
Abdomen/pelvis trauma	2

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

eTable 39. Baseline characteristics and outcomes of patients admitted to the ICU for a non-infectious condition and with genomic response analyzed upon admission, stratified according to the presence and evolution of acute kidney injury

	No AKI (n = 141)	AKI		*P* Value
		Transient AKI (n = 15)	Persistent AKI (n = 66)	
Demographics				
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)	10 (15.2)	.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)[a]	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)[a]	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[b]	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

	No AKI (n = 141)	AKI		*P* Value
		Transient AKI (n = 15)	Persistent AKI (n = 66)	
Outcome				
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.

[c] Between inclusion and day-90.

[d] 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

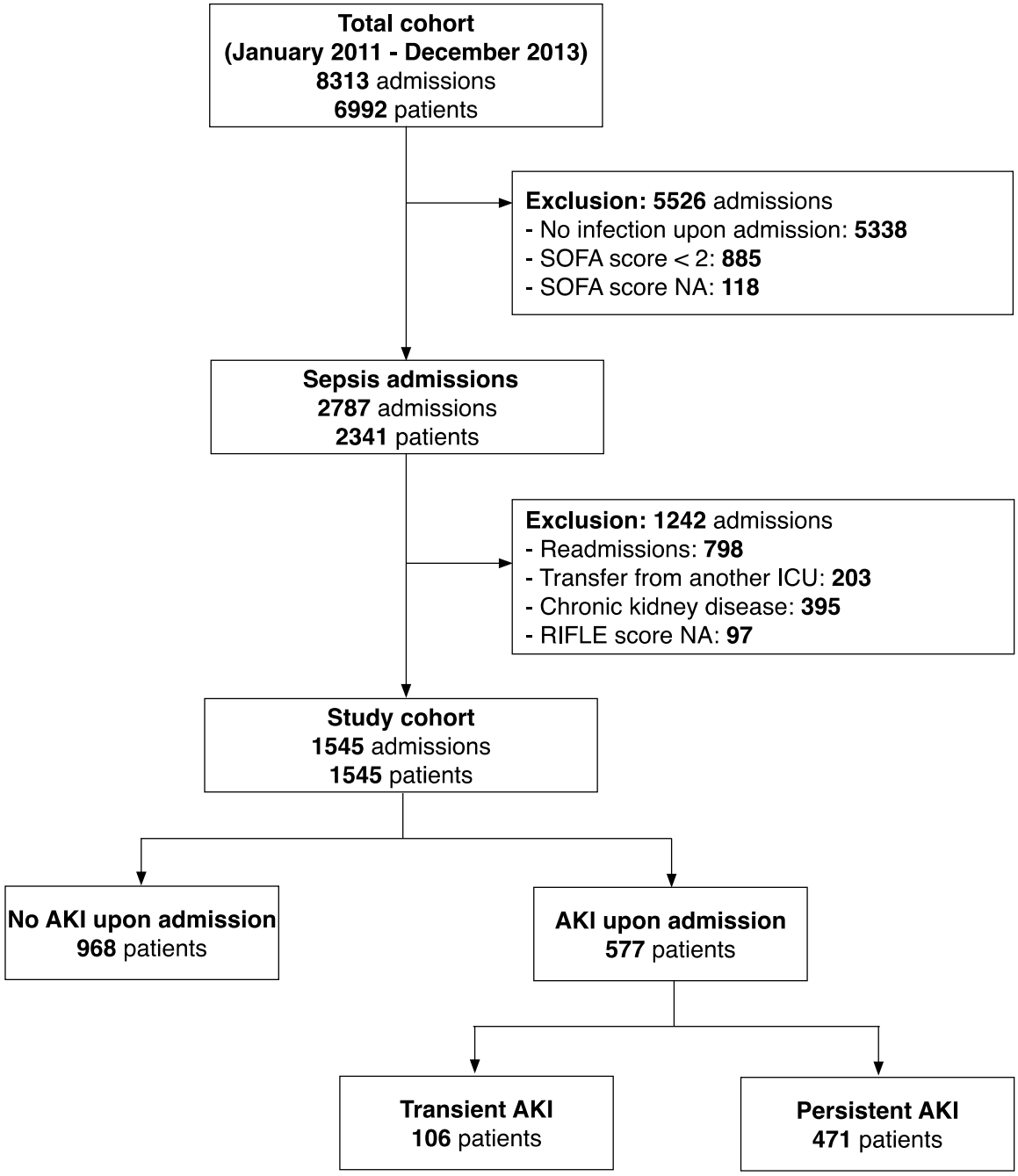
Surgical diagnoses	*N*
Abdominal surgery	**40**
GI cancer	27
GI surgery, other	6
GI Perforation/rupture	4
GI bleeding	2
Cholecystectomy	1
Cardiothoracic surgery	**32**
CABG +valve repair/replacement	12
Cardiovascular surgery, other	12
CABG	7
Lung/heart transplant	1
Neurological surgery	**8**
Hemorrhage/hematoma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

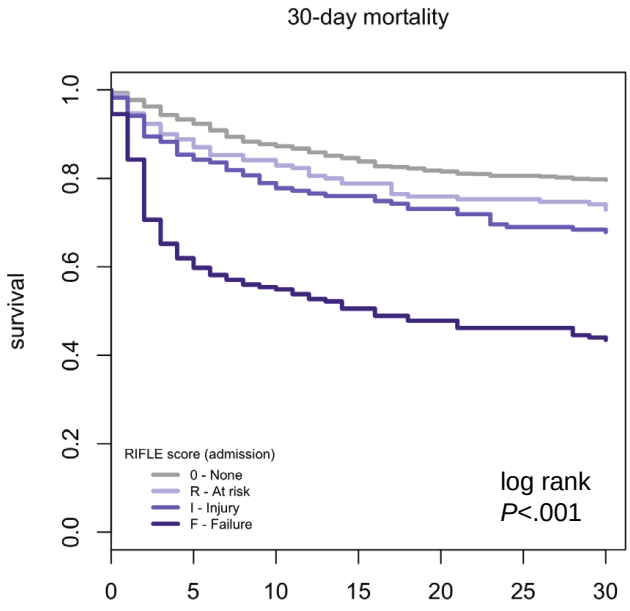
Supplemental figures

eFigure 1. Flow chart of patient inclusion



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).

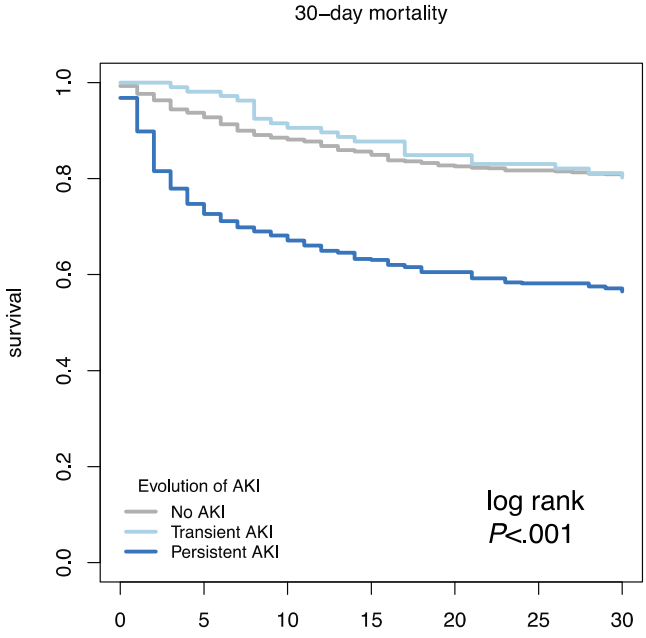
eFigure 2. Kaplan-Meier 30-day survival plot of patients with sepsis stratified according to the severity of acute kidney injury upon admission to the intensive care unit



Number at risk							
0 - None	1020	952	895	863	834	822	814
R - At risk	170	151	143	134	129	128	126
I - Injury	171	146	135	130	125	118	117
F - Failure	184	114	102	93	88	85	81

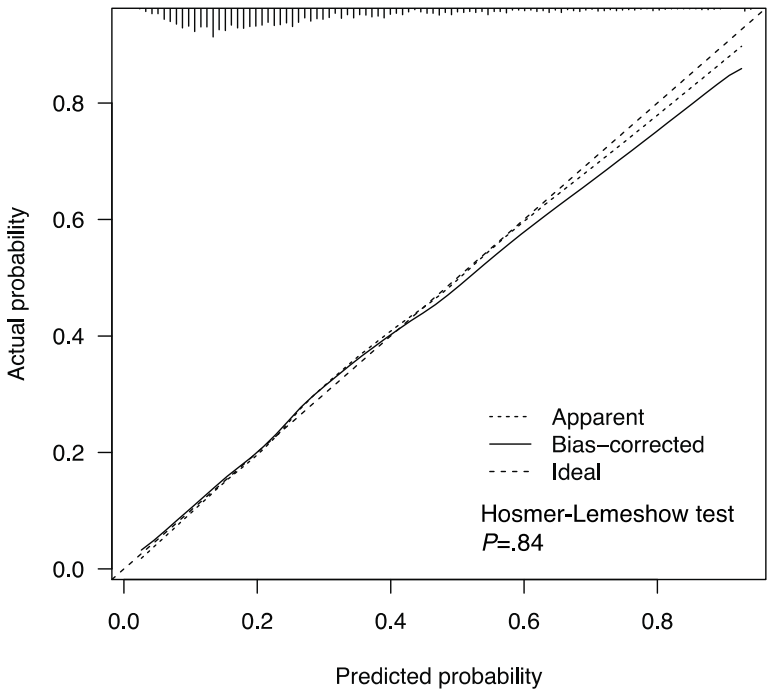
RIFLE, risk, injury, failure, loss, and end-stage kidney disease.

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



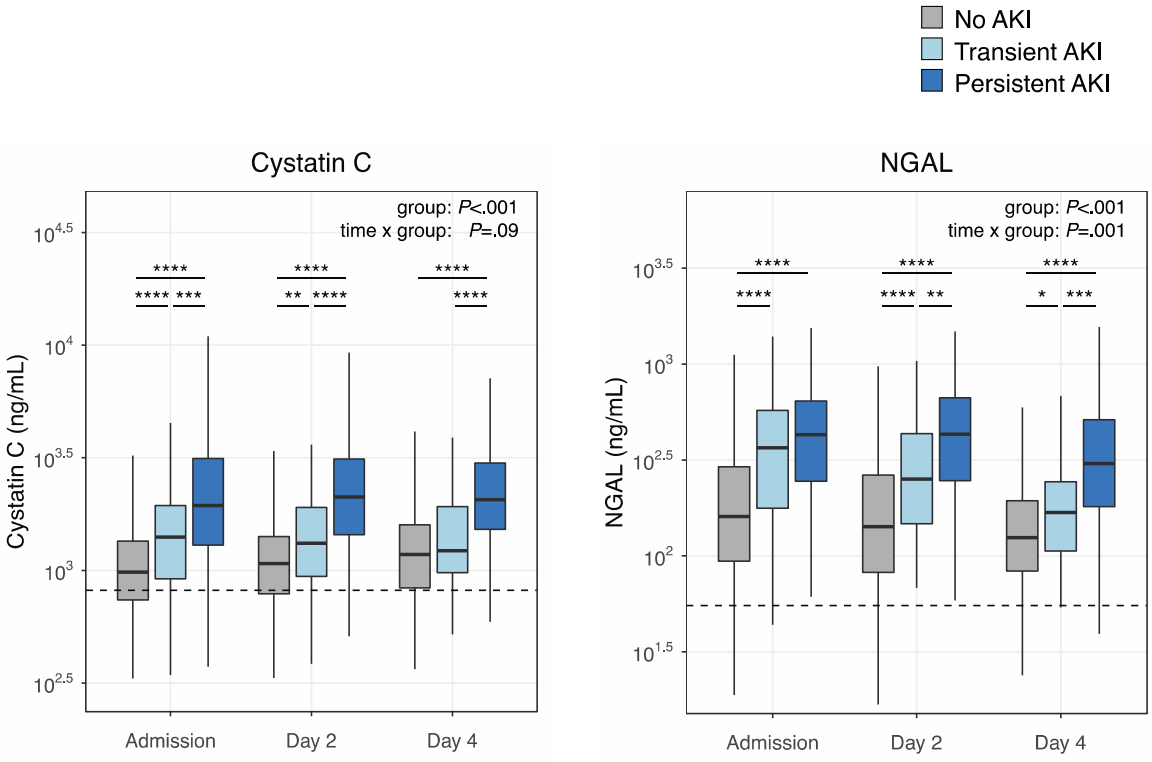
Number at risk							
No AKI	968	907	857	829	801	791	783
Transient AKI	106	104	97	93	90	88	86
Persistent AKI	471	352	321	298	285	274	269

eFigure 4. Calibration plot for the adjusted logistic regression model predicting 30-day mortality



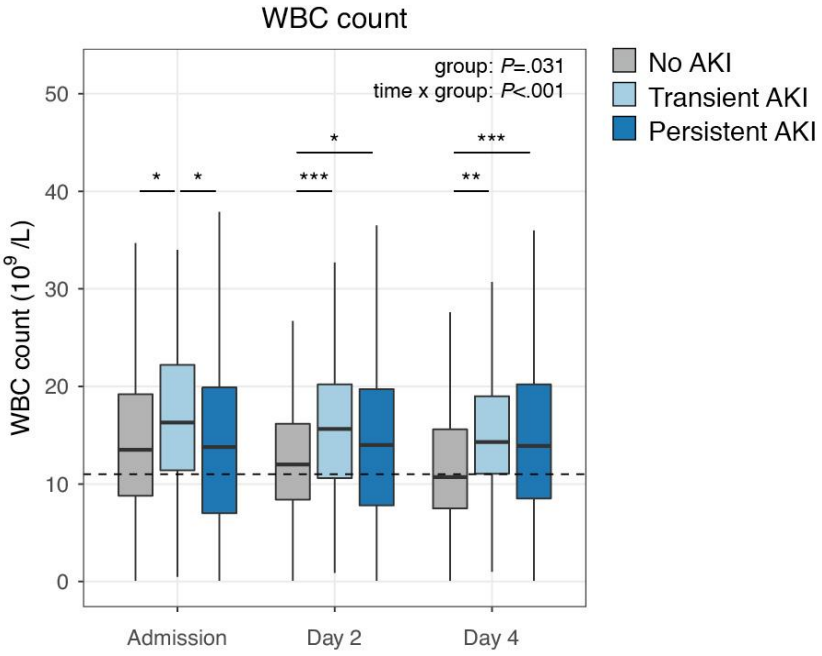
Calibration plot of the logistic regression model for the prediction of 30-day mortality, after adjustment for age, admission RIFLE score, APACHE acute physiology score, source of infection, and modified-Charlson comorbidity index (omitting the age parameter). The Hosmer-Lemeshow test probability denotes 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



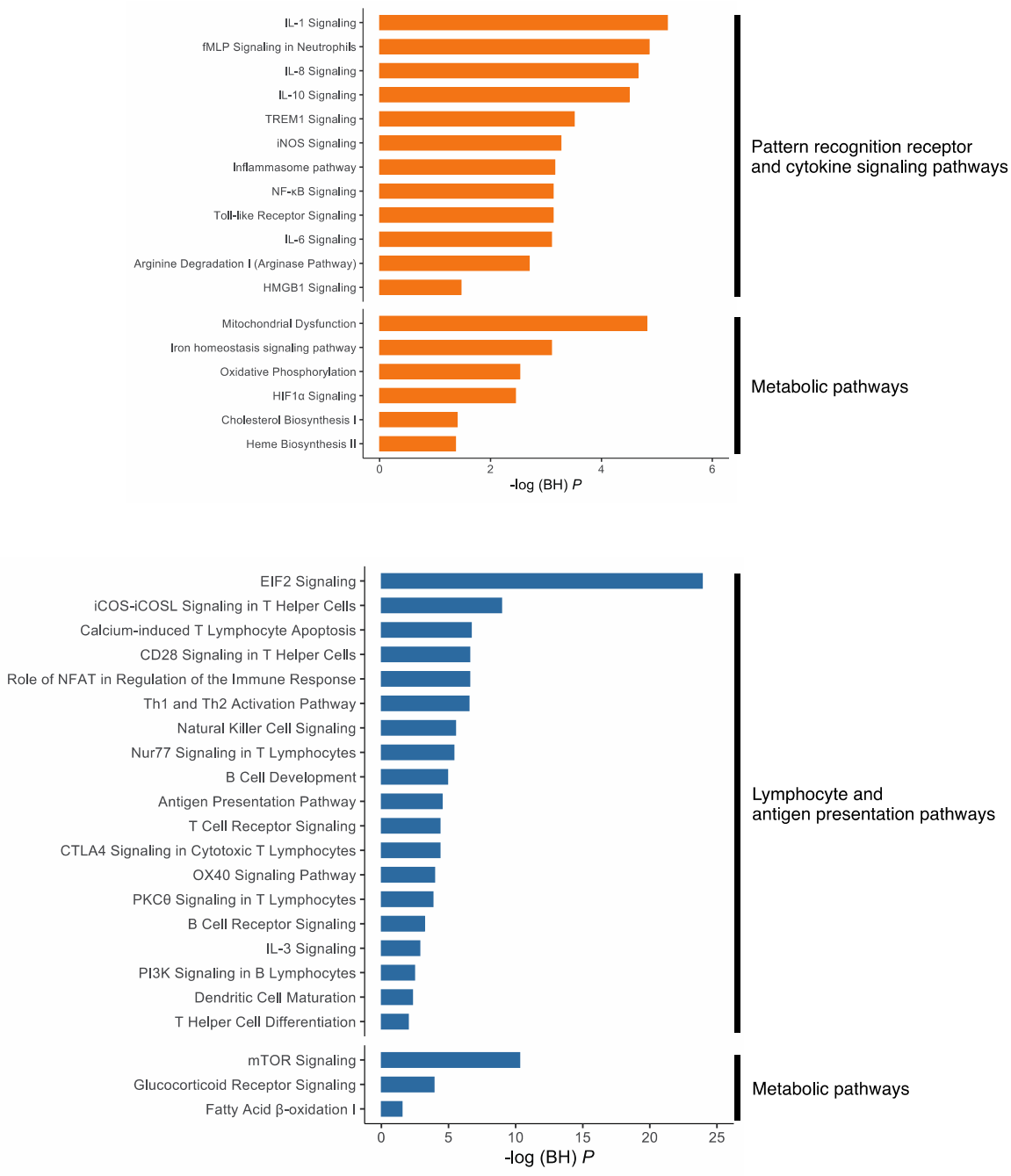
Data are presented as box and whiskers, as specified by Tukey. Dotted lines represent median values obtained in 27 healthy age-matched healthy subjects. Overall *P* values were derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined 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



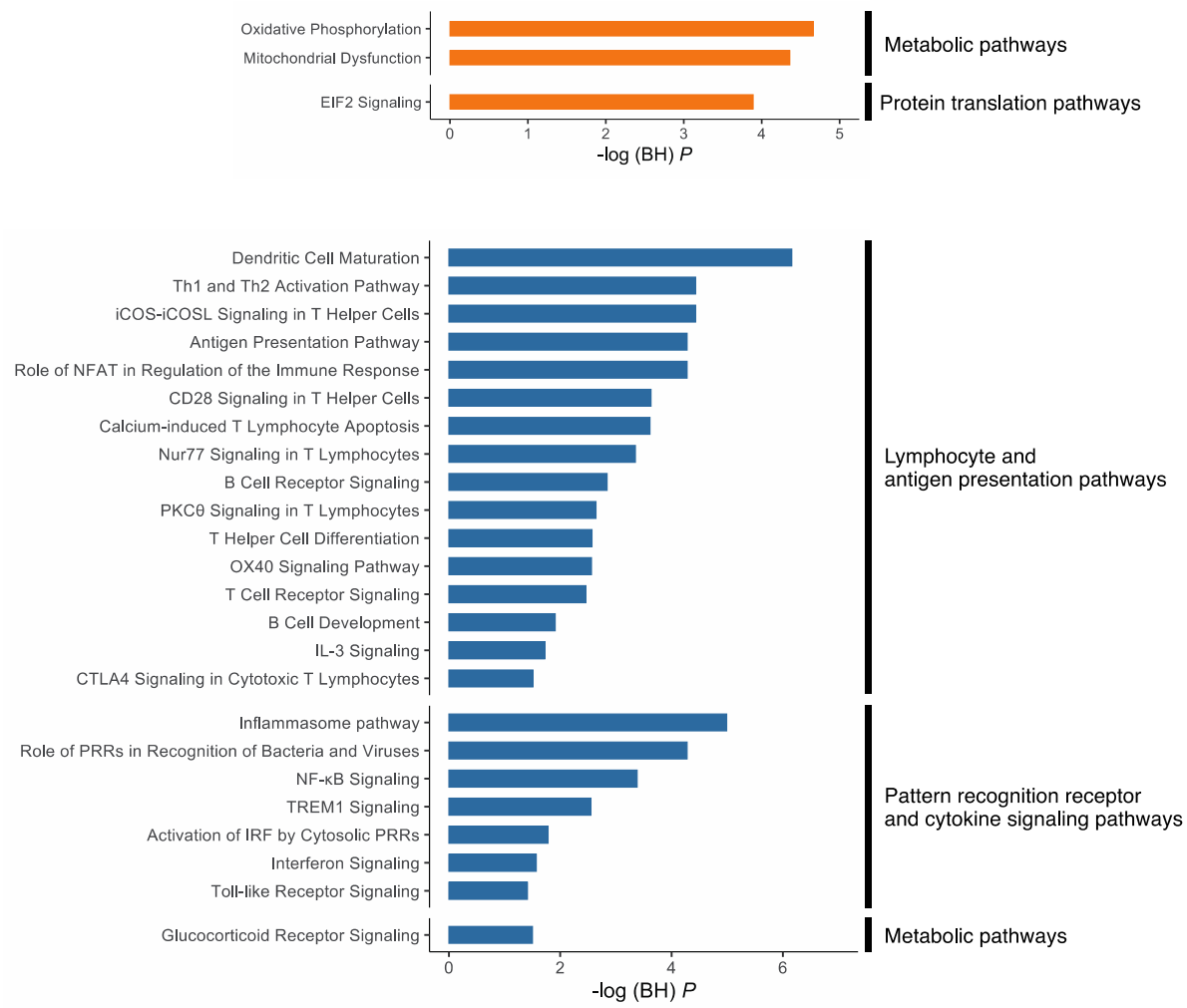
Data are presented as box and whiskers, as specified by Tukey. Dotted line represents the upper laboratory reference value. Overall *P* values were derived from the linear mixed model in which the group, or the interaction of time x group (i.e. the trajectory) were defined as fixed effects, and patient-specific 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*<.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.

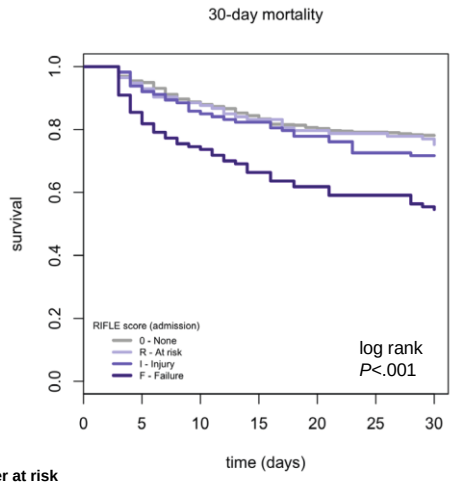
eFigure 8. Transcriptional response in blood leukocytes obtained on admission in sepsis patients with persistent relative to no acute kidney injury



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.

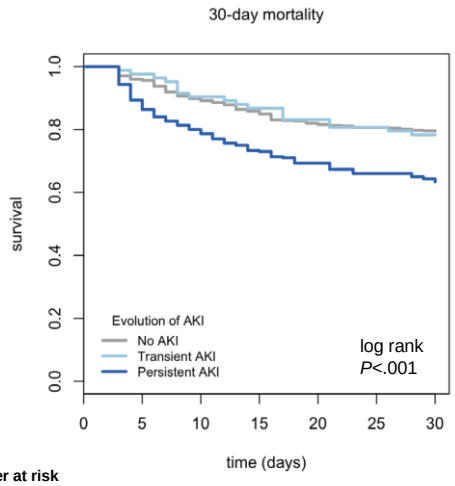
eFigure 9. Kaplan-Meier survival plots of patients with sepsis still present in the intensive care unit on day-4, stratified according to severity and evolution of acute kidney injury

a



Number at risk							
0 - None	590	563	524	498	476	467	461
R - At risk	113	107	100	94	90	89	87
I - Injury	113	106	97	93	88	82	81
F - Failure	110	94	82	73	68	65	61

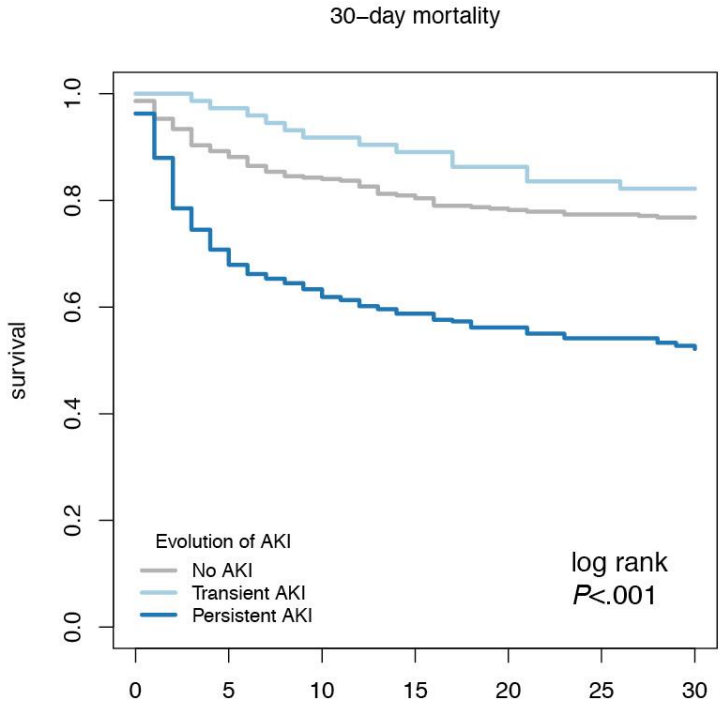
b



Number at risk							
No AKI	543	521	488	466	445	438	432
Transient AKI	83	81	75	72	69	67	65
Persistent AKI	300	268	240	220	208	198	193

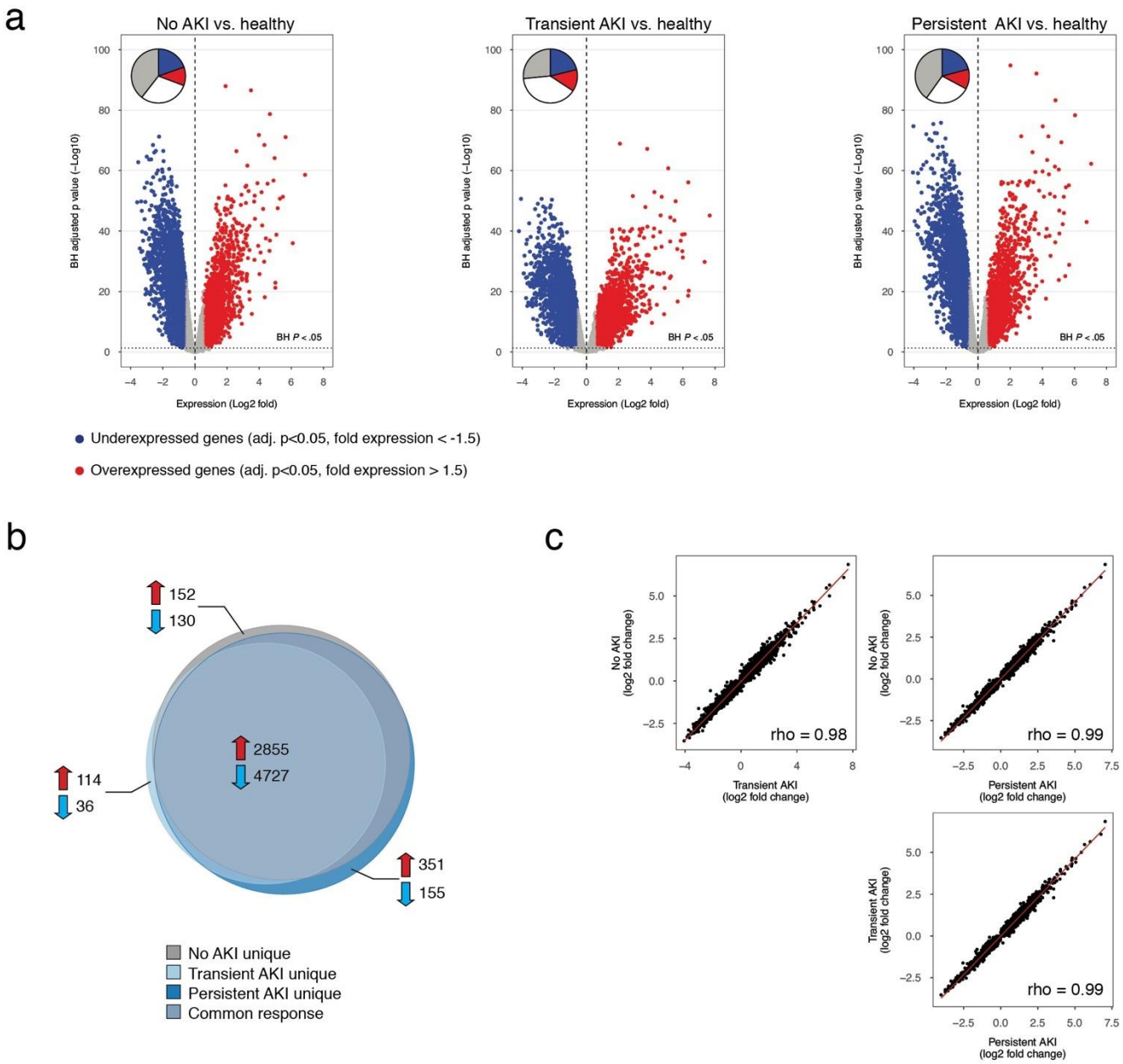
Kaplan-Meier 30-day survival plots according to (**a**) the severity upon admission and (**b**) the evolution of acute kidney injury, in the subgroup of patients still present in the ICU on day 4.

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



Number at risk							
No AKI	362	323	305	293	284	280	278
Transient AKI	73	71	67	65	63	61	60
Persistent AKI	349	247	221	205	196	189	184

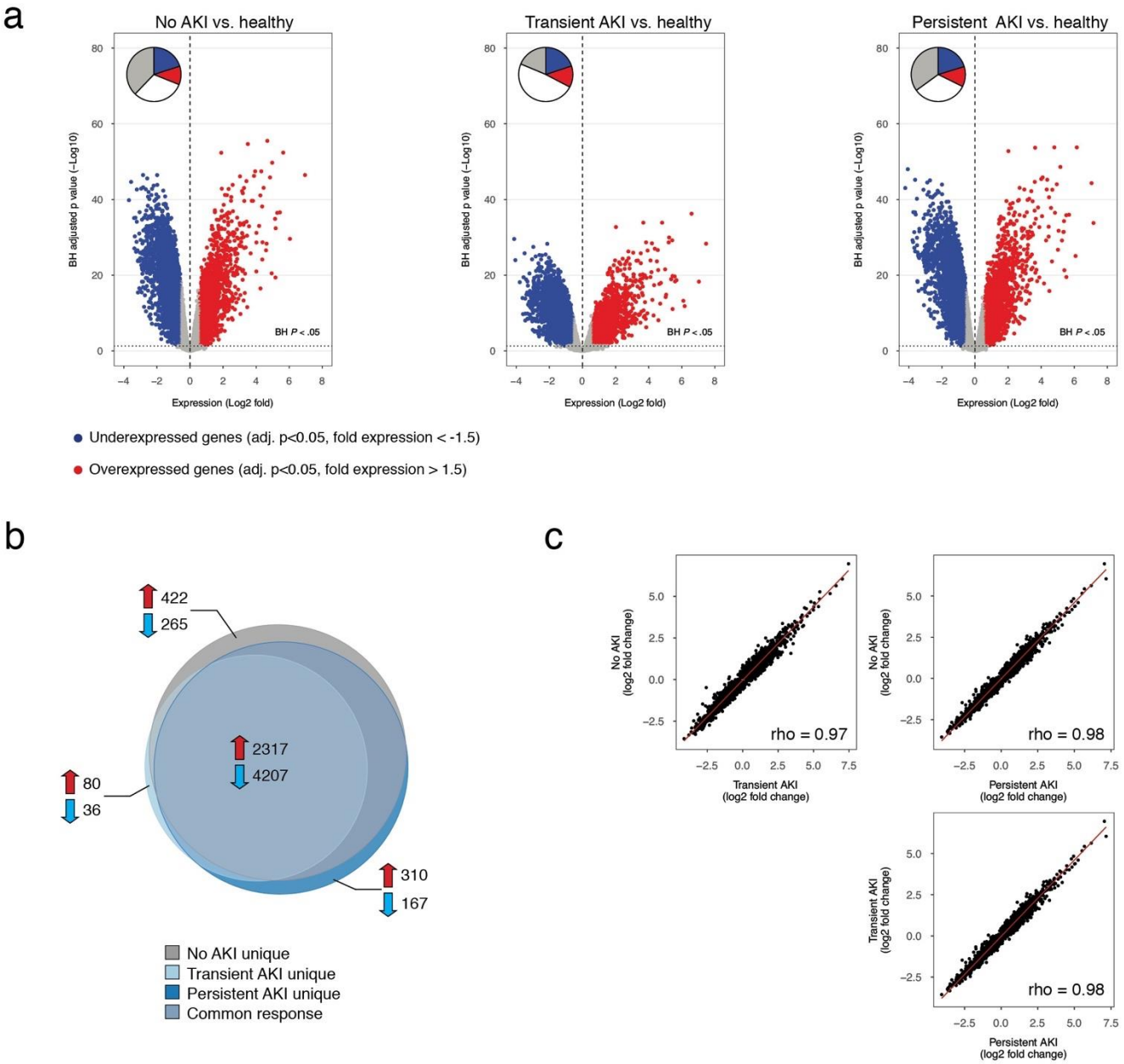
eFigure 11. Leukocyte genomic responses upon admission in patients admitted with septic shock without, transient, or persistent acute kidney injury



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*<.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*<.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 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, 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.

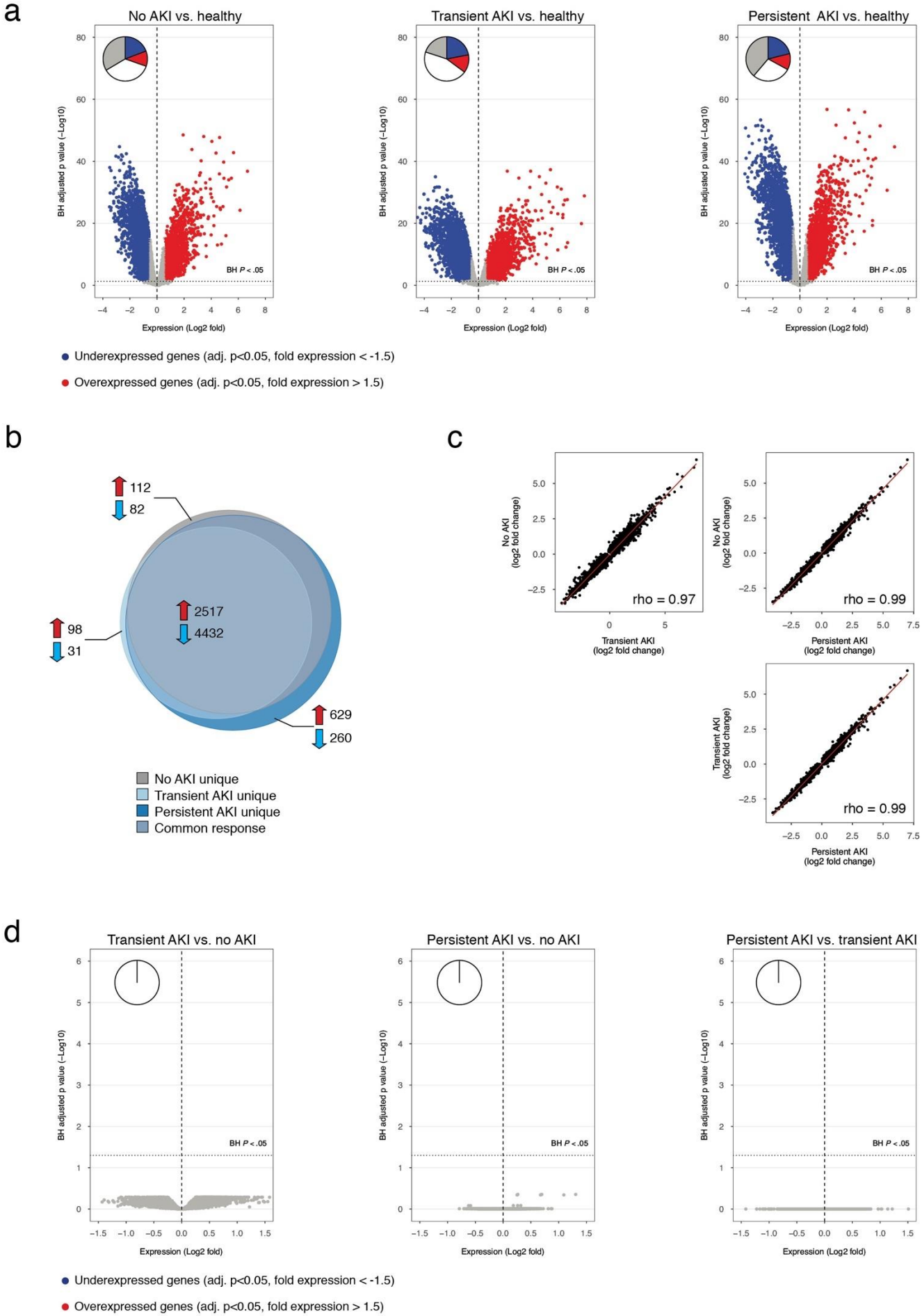
eFigure 12. Leukocyte genomic responses upon admission in patients admitted with septic shock of short duration (< 52 hours) without, transient, or persistent acute kidney injury



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*<.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*<.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 short 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, 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.

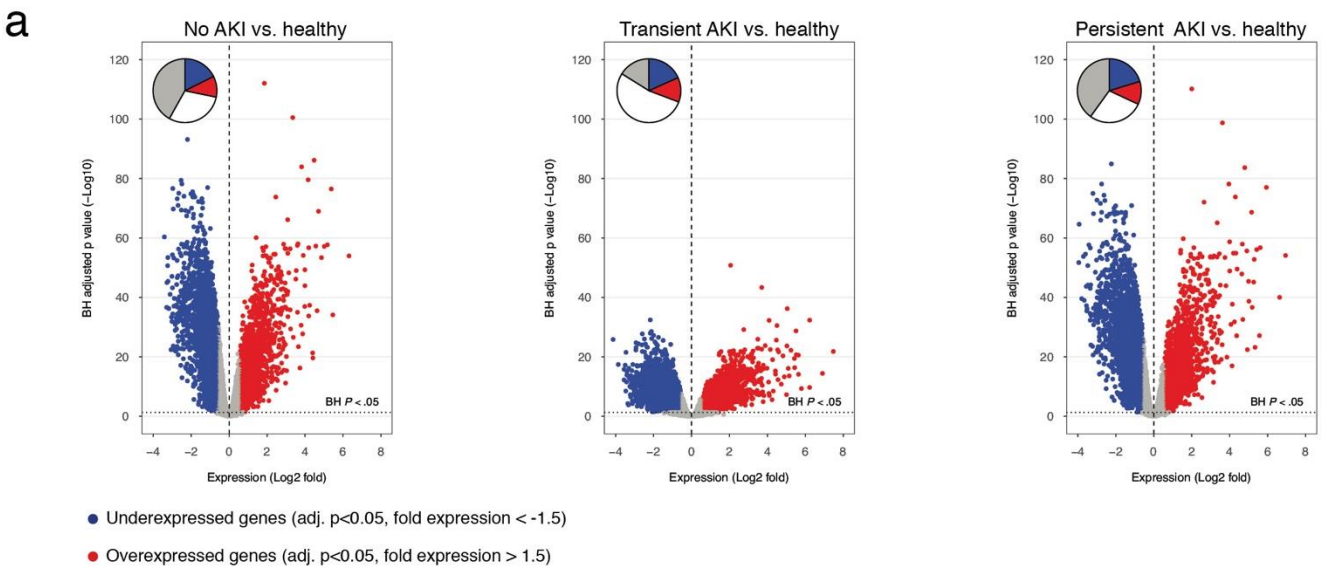
eFigure 13. Leukocyte genomic responses upon admission in patients admitted with septic shock of long duration (≥ 52 hours) without, transient, or persistent acute kidney injury

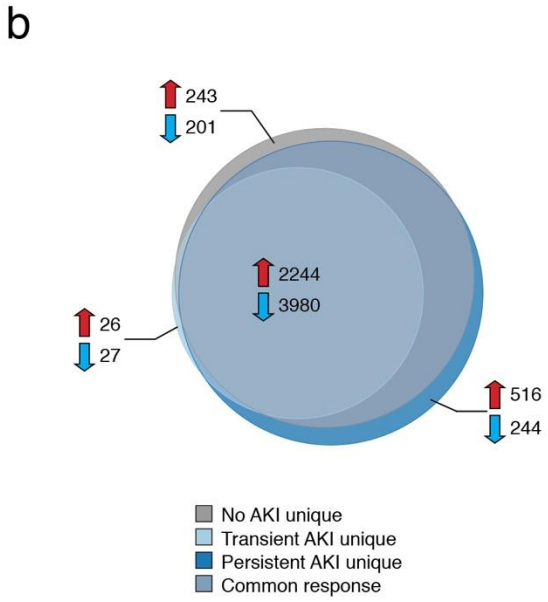


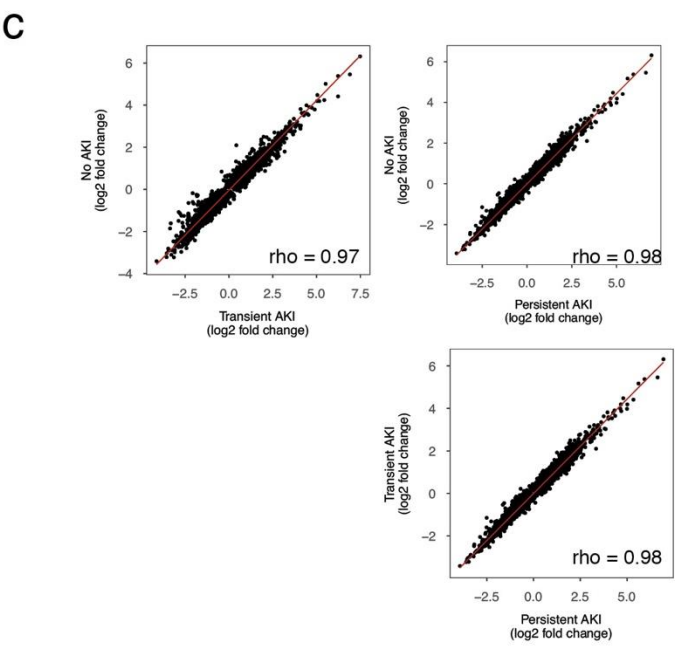
eFigure 13. Leukocyte genomic responses upon admission in patients admitted with septic shock of long duration (≥ 52 hours) without, transient, or persistent acute kidney injury (Legend)

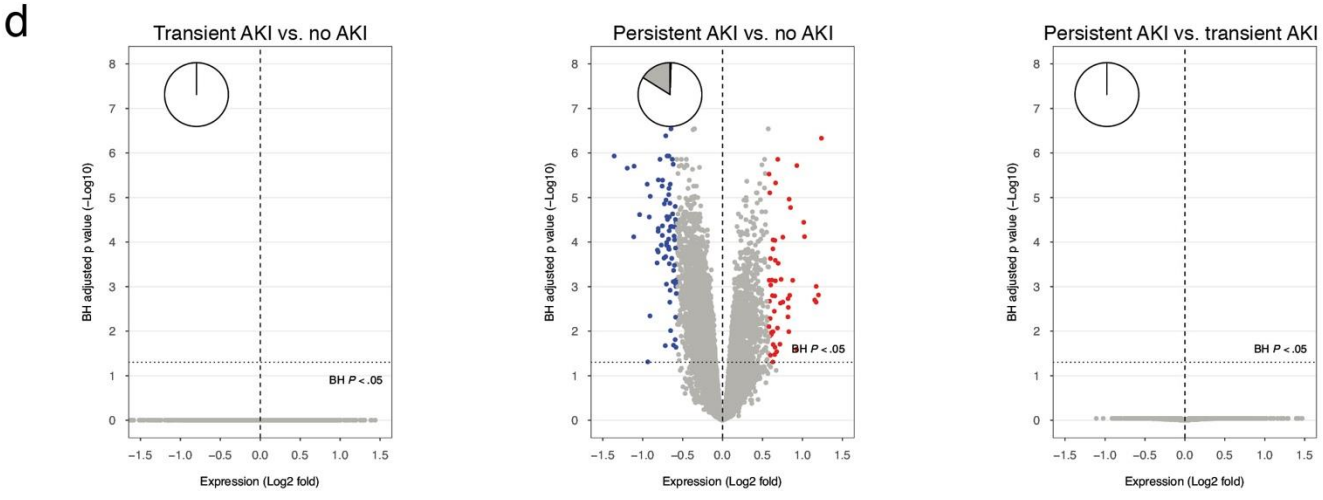
(**a**) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with septic shock of long duration (≥ 52 hours) without acute kidney injury (AKI) on admission and healthy subjects (left), 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)





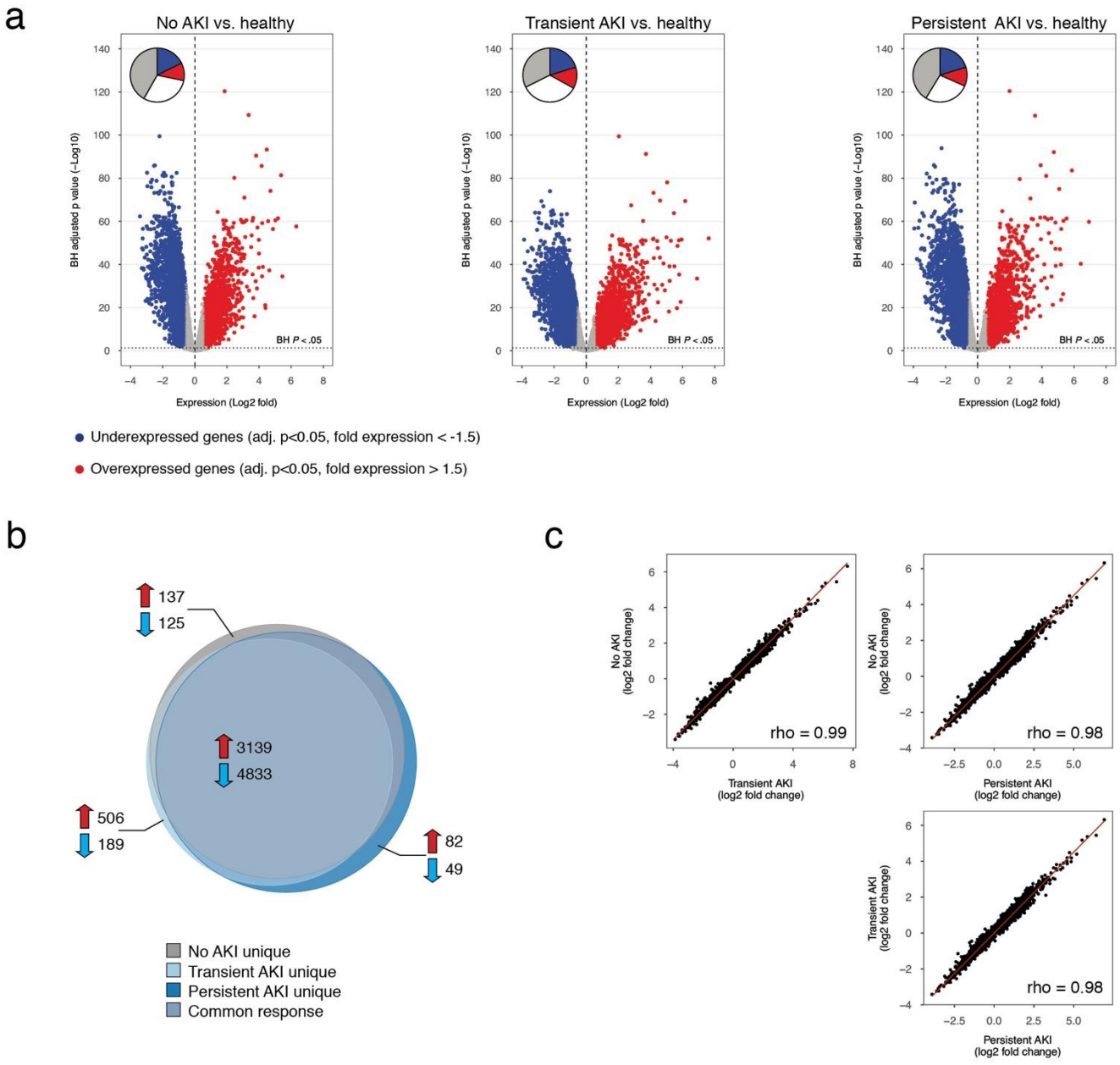




eFigure 14 Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury (RIFLE I and F only) (Legend)

(**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*<.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*<.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 RIFLE I and F only) 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, 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.

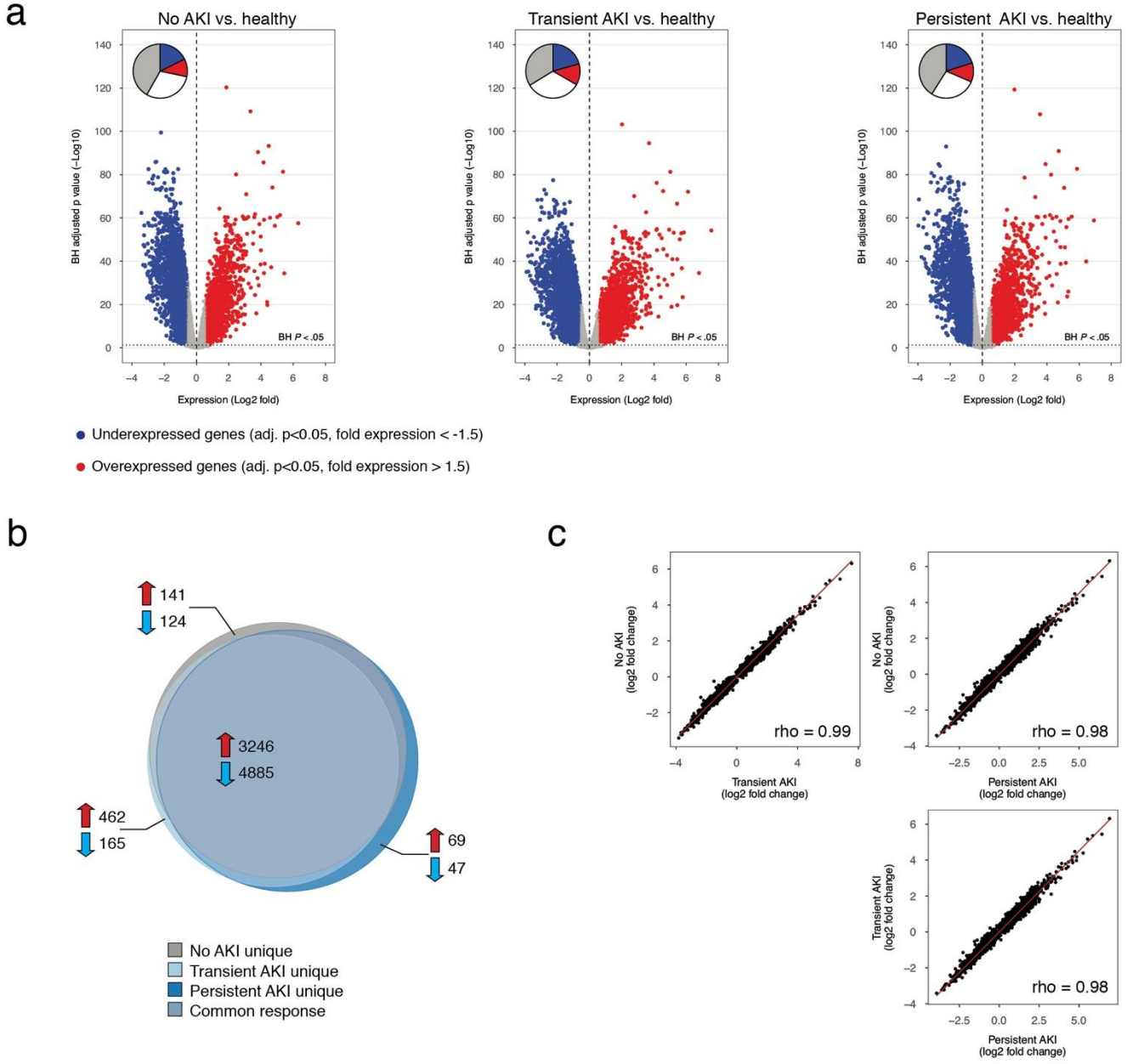
eFigure 15. Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury based on a 72-hour cutoff



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.

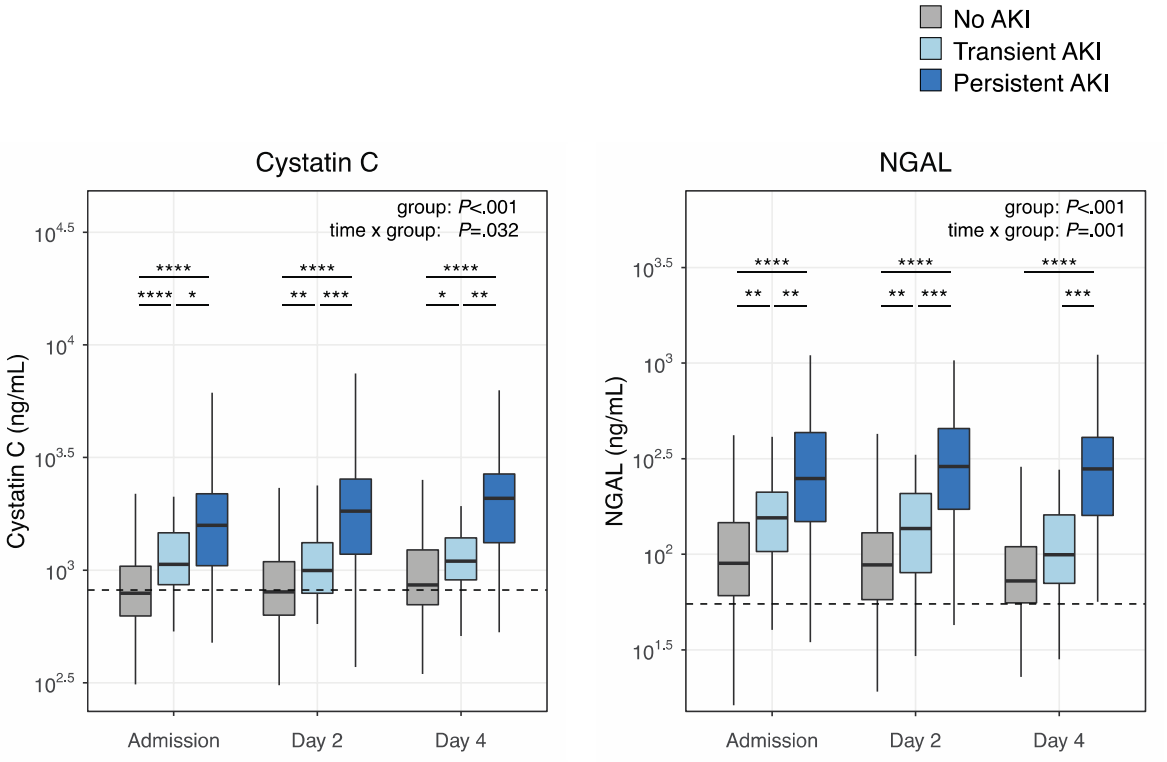
eFigure 16. Leukocyte genomic responses upon admission in patients admitted with sepsis without, transient, or persistent acute kidney injury based on a 96-hour cutoff



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 (Legend)

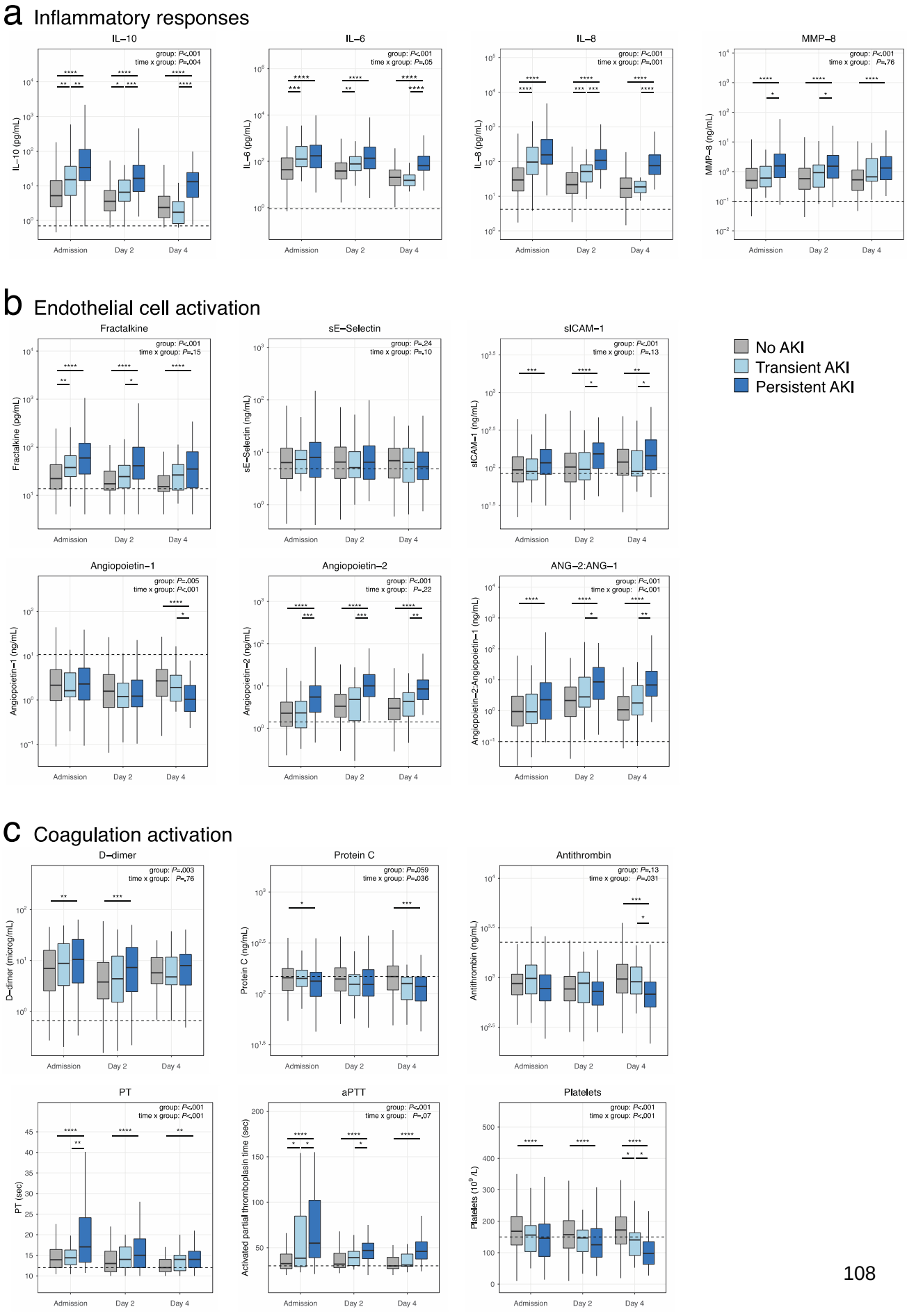
(**a**) Volcano plots illustrating the differences in leukocyte genomic responses (integrating log2 fold changes and multiple-test adjusted probabilities) between patients admitted with sepsis without acute kidney injury (AKI) on admission and healthy subjects (left), between patients with transient 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.

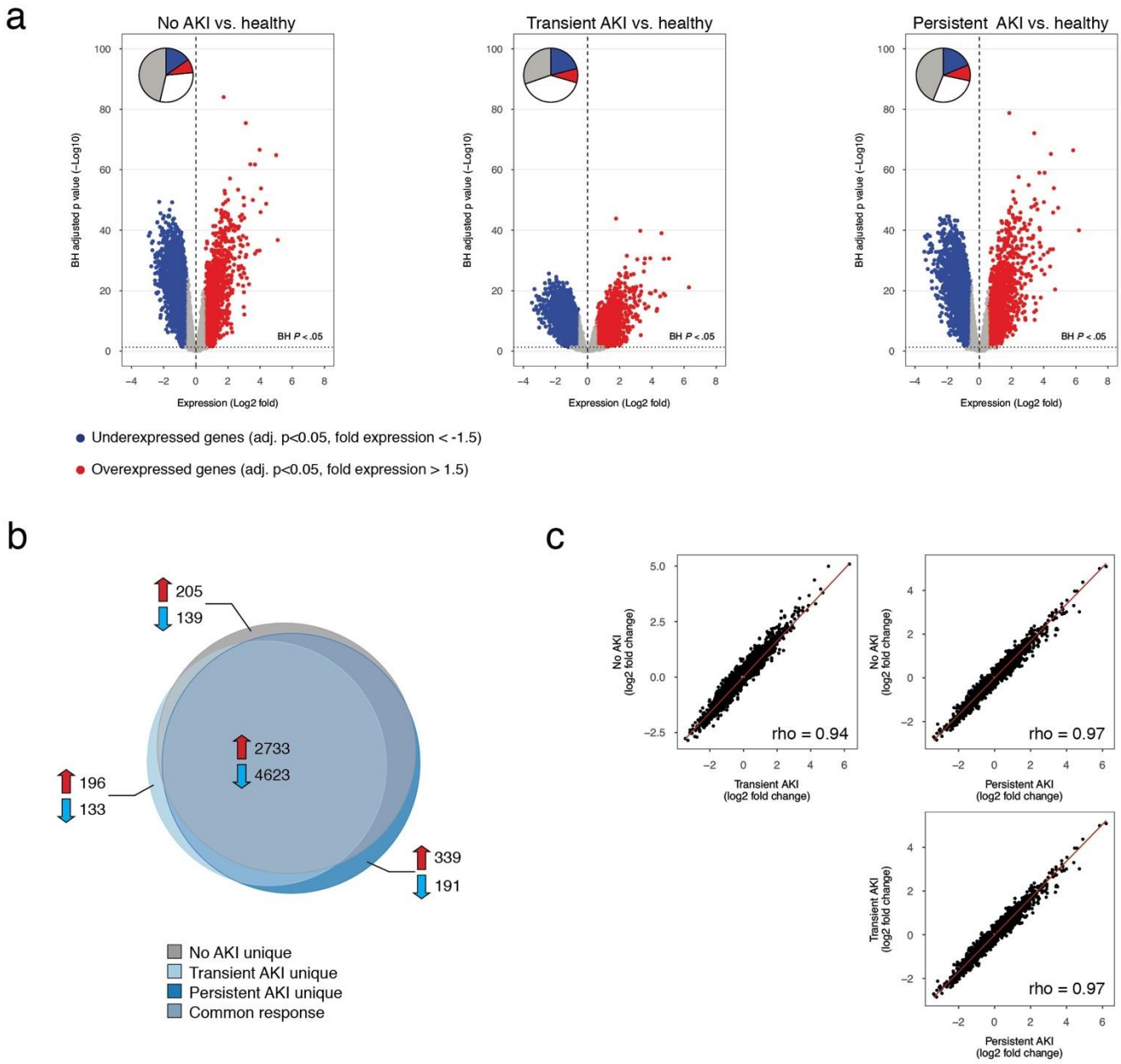
eFigure 18. Host response biomarkers in patients admitted for non-infectious conditions during the first 4 days of ICU stay stratified according to the evolution of acute kidney injury



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



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*<.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*<.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 for a non-infectious condition 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, 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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