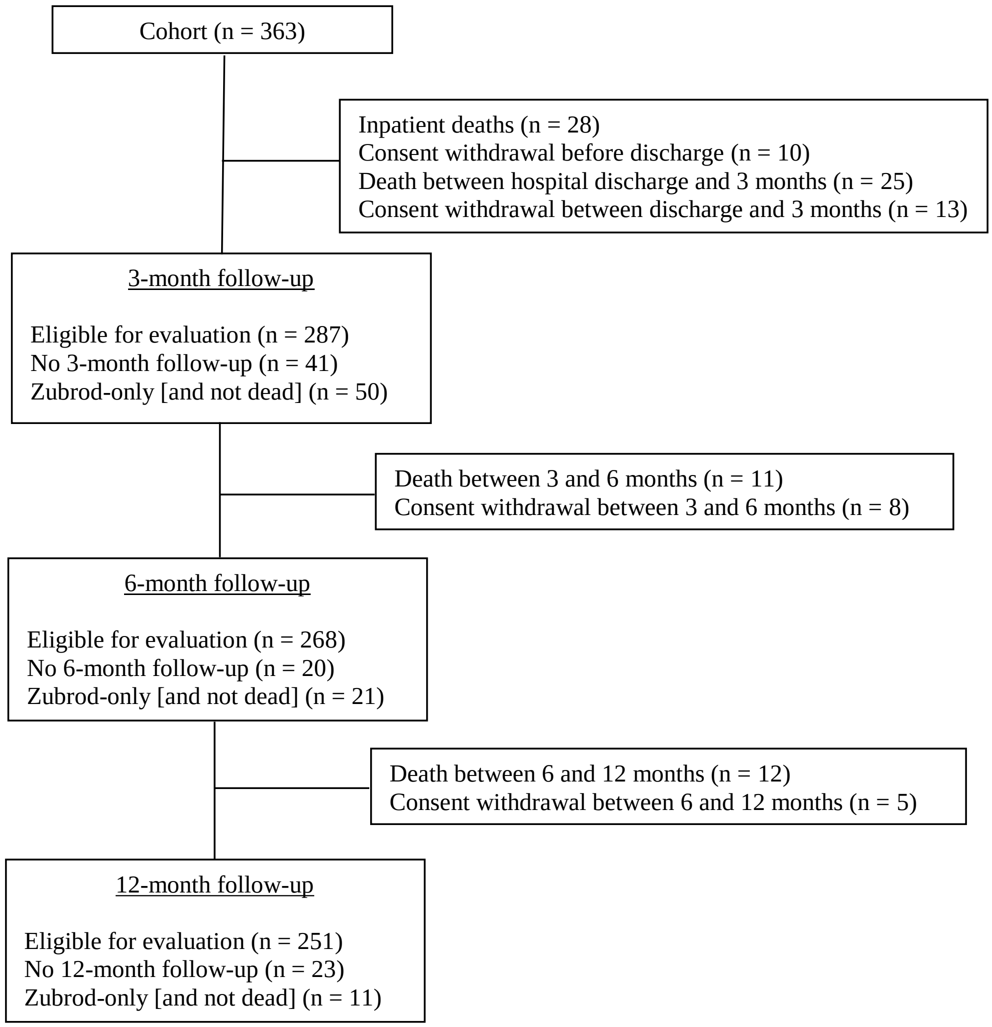
eFigure1. CONSORT diagram.



eTable1. Description of the biomarkers used in this study.

Biomarker type	Role	Category	Cell source	Healthy Controls Median (25th-75th)
Interleukin-6 (IL-6) [1]	Prototypic pro-inflammatory cytokine that is secreted in response to pathogen-associated molecular patterns (PAMPS). Cytokine that has an inhibitory effect on TNFα and IL-1 and activation of IL-10.	Inflammation	Macrophages, adipocytes and myocytes	5 (4, 8) pg/ml [b]
Interleukin-8 (IL-8) [2]	Chemokine, induces neutrophil chemotaxis to the infection site where it stimulates phagocytosis.	Inflammation	Macrophages, endothelial and epithelial cells	7 (5, 8) pg/ml [b]
Monocyte chemoattractant protein 1 (MCP-1) [3]	Induces chemotaxis, mainly of monocytes.	Inflammation	Monocytes, macrophages and dendritic cells	282 (234, 313) pg/ml [b]
C-reactive protein (CRP) [4]	Acute-phase protein secreted in response to cytokines.	Inflammation	Hepatocytes	11.1 (5, 19.8) mg/l [a]
soluble programmed death-ligand 1 (sPDL-1) [5]	Inhibits the function of T and B cells of producing cytokine production, indicates immunosuppression.	Immunosuppression	Macrophages, T cells, B cells, epithelial and endothelial cells	54 (48, 64) pg/ml [b]
Absolute lymphocyte count (ALC) [6]	Indicator of immune suppression, and lower levels are linked to recurring infections.	Immunosuppression	Lymphocytes	1-3.2 (cells/cubic mm)
Absolute neutrophil count (ANC) [7]	Indicator of immune suppression, and higher levels are linked to sepsis severity.	Immunosuppression		1.7-7 (cells/cubic mm)
Interleukin-10 (IL-10) [8]	Produced by immune cells, inhibits the production of pro-inflammatory cytokines.	Immunosuppression	Monocytes	17.4 (10.9, 33.2) (pg/ml)[b]
Glucagon-like peptide-1 (GLP-1) [9]	Peptide hormone with anti-inflammatory properties, and GLP- 1 increase is mediated by excrection of IL-6, and is associated with severity of sepsis.	Stress metabolism	intestinal enteroendocrine L-cells	0-15 (pM)
Albumin [10-11]	Transports hormones, bilirubin and fatty acids, maintains oncotic pressure. Constitutive protein of which production in decreased during an acute stress response.	Stress metabolism	Hepatocytes	3.4-5.4 (g/dl)

Insulin-like growth factor 1 (IGF-1) [12]	Regulates cell metabolism, growth, proliferation and apoptosis in multiple organ systems. IGF-1 is abundant in the circulation and binds to IGFB.	Catabolism	Hepatocytes	59.6 (44.9, 71.4) (ng/ml)[b]
Insulin-like growth factor binding protein (IGFBP-3) [13]	Is a circulating carrier of IGF-1 and regulates its biological effects by sequestering IGF-1 into a circulating reservoir, and thus reduces the free fraction of bioactive IGF in the blood.	Catabolism	Hepatocytes	2000.7 (1537.9, 2215.3) (ng/ml)[b]
Soluble vascular endothelial growth factor receptor-1 (Flt-1) [14]	Modulates endothelial cell proliferation, inhibits angiogenesis and upreagulates VEGF.	Angiogenesis	Endothelial cells	77 (64.1, 80.3) (pg/ml)[c]
Vascular endothelial growth factor (VEGF) [14]	Promotes angiogenesis, proliferation, migration and survival of endothelial cells, and contributes to inflammation and coagulation.	Angiogenesis	Macrophages, platelets, keratinocytes, endothelial cells	391.4 (206.4, 571.9) (pg/ml) [c]
Angiopoietin 2 (Ang2) [14]	Growth factor regulated by inflammatory signaling. Promotes angiogenesis in the presence of VEGF, and can potentiate apoptosis in the absence of vascular endothelial growth factor.	Angiogenesis	Endothelial cells	1709 (1405, 2356) (ng/mL) [c]
Interferon gamma-induced protein 10 (IP-10) [15]	Chemokine induces chemotaxis, mainly of monocytes/macrophages, T cells and dendritic cells; Inhibits angiogenesis.	Inflammation	Monocytes and endothelial cells	303.82 (247.02, 528.8) pg/ml [b]

eTable2. Updated baseline demographics and predisposition characteristics of by age groups.

Age Groups n (%)	Young 75 (21%)	Middle-aged 143 (39%)	Older 145 (40%)
Male, n (%)	39 (52)	76 (53)	81 (56)
Age in years, median (IQR 25th, 75th)	36 (28, 43)[a,b]	58 (53, 62)[c]	72 (69, 76)
Race, n (%)			
Caucasian (White)	67 (89)	124 (87)	133 (92)
African American	7 (9)	18 (13)	10 (7)
American Indian	1 (1)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	1 (1)
Other	0 (0)	1 (1)	0 (0)
Unknown	0 (0)	0 (0)	1 (1)
Ethnicity, n (%)			
Hispanic or Latino	5 (7)	4 (3)	1 (1)
Not Hispanic or Latino	70 (93)	139 (97)	144 (99)
BMI, median (25th, 75th)	30.3 (25.8, 40.2)[b]	29.8 (25.5, 39.1)[c]	28.3 (24.4, 34)
Morbid obesity n (%)	19 (25)[b]	31 (22)[c]	15 (10)
Comorbidities, n (%)			
Hypertension	24 (32)[a,b]	88 (62)[c]	114 (79)
Coronary artery disease	4 (5)[b]	24 (17)[c]	61 (42)
Diabetes	12 (16)[a,b]	56 (39)	56 (39)
Chronic lung disease	1 (1)[a,b]	28 (20)	41 (28)
Atrial fibrillation	0 (0)[a,b]	10 (7)[c]	32 (22)
Chronic renal disease	4 (5)[b]	19 (13)	27 (19)
Heart failure	2 (3)[a,b]	15 (11)	30 (21)
Peripheral artery disease	4 (5)[a,b]	9 (6)[c]	31 (21)
Active cancer	6 (8)	26 (18)	25 (17)
Prior Stroke	1 (1)	13 (9)	12 (8)
Substance abuse	7 (9)	15 (11)	11 (8)
Dementia	0 (0)	2 (1)	6 (4)
Liver disease	2 (3)	6 (4)	2 (1)
ESRD	1 (1)	18 (13)[c]	3 (2)
Number of comorbidities (adjudicated), n (%)	[a,b]		
0	38 (51)	21 (15)	6 (4)
1	16 (21)	35 (25)	23 (16)
2	17 (17)	35 (25)	33 (21)
≥3	4 (5)	52 (36)	83 (57)
Reason for Hospital Admission, n (%)			
Planned Surgery	13 (17)	27 (19)	29 (20)
Trauma	11 (15)	14 (10)	11 (8)
Active Infection	48 (64)	89 (62)	89 (61)
Non-Infectious / Chronic Problems	3 (4)	13 (9)	16 (11)
Emergency surgery (within 24 hrs), n (%)	44 (59)	78 (55)	65 (45)
Sepsis present on admission (≤48 hrs), n (%)	51 (68)	92 (64)	83 (57)
Hospital-acquired sepsis (>48 hrs), n (%)	24 (32)	51 (36)	62 (43)
Type of Infection n (%)			
Intra- abdominal	13 (17)[b]	38 (27)[c]	54 (37)
Surgical Site Infection	24 (32)[b]	33 (23)	27 (19)
Pneumonia	11 (15)	24 (17)	25 (17)
Necrotizing Soft Tissue Infection	10 (13)[b]	24 (17)[c]	8 (6)
Urosepsis	10 (13)	13 (9)	19 (13)
Other	6 (8)	9 (6)	10 (7)
Catheter Related Blood Steam Infection	1 (1)	2 (1)	2 (1)

Sepsis severity, n (%)			
Sepsis	37 (48) [a,b]	39 (27)	34 (24)
Severe Sepsis	30 (40)	65 (46)	61 (42)
Septic Shock	8 (12) [a,b]	39 (27)	50 (34)
APACHE II Score (24 hrs), median (IQR 25th, 75th)	12 (7, 17) [a,b]	15 (11, 22) [c]	20 (16, 26)
SOFA score (24 hrs), median (IQR 25th, 75th)	6 (3, 7) [a,b]	7 (5, 9) [c]	8 (6, 10)
Culture Negative	20 (27)	53 (37)	58 (40)
Culture Positive	55 (73)	90 (63)	87 (60)
Bacterial – gram positive	10 (13)	21 (15)	24 (17)
Bacterial – gram negative	22 (29)	38 (27)	34 (25)
Fungal	2 (3)	5 (4)	3 (2)
Polymicrobial	21 (28)[b]	26 (18)	26 (18)
Sepsis Source Control Procedure, n (%)	56 (71)	105 (73)	93 (63)
Invasive procedures	31 (41)	74 (52)	72 (50)
Non-invasive procedures	25 (33)	31 (22) [c]	21 (15)

BMI = Body Mass Index, IQR = Interquartile Range, APACHE II = Acute Physiology + Age + Chronic Health Evaluation, SOFA = the Sequential Organ Failure Assessment. Statistical difference was labeled as [a] - young vs. middle-aged, [b] - young vs. older adults and [c] - middle-aged vs. older adults, with statistical significance set at $p<0.05$.

eTable3. Hospital outcomes, clinical trajectory and discharge disposition for overall and by age group.

Age Groups n (%)	**Young 75 (21%)**	**Middle-aged 143 (39%)**	**Older 145 (40%)**
Need for mechanical ventilation, n (%)	40 (53)[b]	90 (63)	111 (77)
Ventilator free days (30 days), median (IQR 25th, 75th)	26 (26, 30)[b]	25 (21, 28)[c]	24 (17.5, 30)
ICU length of stay, median (IQR 25th, 75th)	5 (3, 12)[b]	7 (3, 17)[c]	9 (4, 17)
Hospital free days (365 days), median (IQR 25th, 75th)	347 (321, 356)[b]	340 (307, 354)	330 (68, 347)
Secondary infections/patient, mean (SD)	0.4 (0.8)[b]	0.5 (0.9)	0.6 (0.8)
Secondary infections/100 hospital days, mean (SD)	2.4 (6.7)[b]	1.7 (3.2)	2.6 (4.5)
AKI, n (%)	35 (47)	63 (44)	89 (61)
KDIGO Stage 1	16 (21)	34 (24)	35 (24)
KDIGO Stage 2	10 (13)	27 (19)	29 (20)
KDIGO Stage 3	9 (12)	15 (11)	25 (17)
Multiple organ failure (MOF) frequency, n (%) – by Denver	4 (5)[b]	18 (13)	31 (21)
30-day mortality, n (%)	4 (5)[b]	5 (4)[c]	24 (17)
Clinical Trajectory, n (%)			
Early Death	2 (3)	3 (2)	9 (6)
Chronic Critical Illness	15 (20)[b]	48 (34)	61 (42)
Rapid Recovery	58 (75)[b]	92 (64)	75 (52)
Discharge disposition, n (%)			
"Good" Disposition	63 (84)[a,b]	90 (63)[c]	54 (37)
Home	22 (34)[b]	30 (21)[c]	13 (10)
Homecare	36 (48)[b]	49 (34)[c]	24 (17)
Rehab	0 (0)[b]	11 (8)	15 (10)
"Poor" Disposition	12 (19)[a,b]	53 (37)[c]	82 (62)
Long Term Care Hospital	5 (7)[b]	19 (13)	30 (21)
Skilled Nursing	0 (0)[a,b]	21 (15)	32 (22)
Another Hospital	4 (5)	6 (4)	3 (2)
Hospice	0 (0)	2 (1)	6 (4)
Death	3 (4)	5 (4)[c]	20 (14)
Number of readmissions, mean (SD)	1 (2)	1 (2)	1 (1)

IQR = Interquartile Range, SD = standard deviation, KDIGO = Kidney Disease: Improving Global Outcomes. Statistical difference was labeled as [a] - young vs. middle-aged, [b] - young vs. older adults and [c] - middle-aged vs. older adults, with statistical significance set at $p<0.05$.

eTable4. Long-term follow-up of physical function and cognitive status for overall and by age group.

Age Groups n (%)		**Young 75 (21%)**	**Middle-aged 143 (39%)**	**Older 145 (40%)**
Physical function				
Total SPPB				
3 months		8.0 ± 0.9[b]	5.4 ± 0.6[c]	3.3 ± 0.6
6 months		8.5 ± 1.1[b]	5.9 ± 0.7	3.4 ± 0.7
12 months		8.1 ± 1.5	5 ± 0.9	5.1 ± 1.1
Handgrip strength				
3 months		30.6 ± 2.3[a,b]	20.8 ± 2.4	27.2 ± 5.0
6 months		47.6 ± 6.0[a,b]	25.5 ± 1.3	23 ± 1.1
12 months		38 ± 2.4[a,b]	27.6 ± 1.4[c]	18.9 ± 2.2
Cognitive function				
Hopkins Verbal Learning Test				
3 months				
	Total recall	25.8 ± 1.0[a,b]	20.8 ± 1.0	18.7 ± 0.9
	Delayed recall	9.5 ± 0.5[a,b]	6.5 ± 0.6	5.4 ± 0.6
	Retention	91.9 ± 2.6[a,b]	73.1 ± 5.3	65.8 ± 6.4
6 months				
	Total recall	26.3 ± 0.9[a,b]	23.3 ± 0.6[c]	18.6 ± 1.6
	Delayed recall	9.3 ± 0.4[a,b]	8 ± 0.3[c]	5.4 ± 0.7
	Retention	93 ± 1.6[b]	86.7 ± 2.8[c]	64.1 ± 7.9
12 months				
	Total recall	27.3 ± 0.9[a,b]	21.9 ± 1.8	20.8 ± 1.3
	Delayed recall	9.7 ± 0.3[a,b]	6.5 ± 1.1	6.8 ± 0.5
	Retention	94.5 ± 2.5[a]	67.1 ± 10.9	80.9 ± 5.0
COWA				
3 months		40.4 ± 1.9[a,b]	29.4 ± 2.2	28.2 ± 1.7
6 months		38.1 ± 1.4[a,b]	33.7.5 ± 1.4	27.5 ± 1.7
12 months		37.4 ± 1.9[b]	31.5 ± 5.7	27 ± 2.4
MMSE				
3 months		90.3 ± 2.3[b]	84.5 ± 2.7	82.4 ± 3.0
6 months		94.8 ± 1.5[a,b]	90.1 ± 1.2[c]	78.9 ± 2.5
12 months		92.5 ± 2.5[b]	87.1 ± 4.3	85.4 ± 2.1

SPPB=short physical performance battery, COWA = Controlled Oral Word Association, MMSE = mini-mental state examination. Statistical difference was labeled as [a] - young vs. middle-aged, [b] - young vs. older adults and [c] - middle-aged vs. older adults, with statistical significance set at $p<0.05$.

eTable5. Amount of organ failures and ventilator use on day 14.

Age groups **N (%)**	**Young** **75 (34%)**	**Older** **145 (66%)**	**Older RAP** **75 (55%)**	**Older CCI** **61 (45%)**
Organ system dysfunction by SOFA on day 14, n (%)				
Pulmonary	3 (4)	14 (10)	0 (0)	11 (18)
CNS	3 (4)	12 (8)	0 (0)	7 (11)
Cardiovascular	2 (3)	13 (9)	0 (0)	11 (18)
Renal	22 (29)	54 (37)	30 (40)	18 (30)
Coagulation	1 (1)	6 (4)	0 (0)	4 (7)
Hepatic	1 (1)	3 (2)	0 (0)	2 (3)
Ventilated on day 14, n (%)	2 (3)	17 (12)	0 (0)	17 (28)

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