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The clinical relevance of oliguria in the critically ill patient: analysis of a large observational database

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Abstract

Background: Urine output is widely used as one of the criteria for the diagnosis and staging of acute renal failure, but few studies have specifically assessed the role of oliguria as a marker of acute renal failure or outcomes in general intensive care unit (ICU) patients. Using a large multinational database, we therefore evaluated the occurrence of oliguria (defined as a urine output < 0.5 ml/kg/h) in acutely ill patients and its association with the need for renal replacement therapy (RRT) and outcome.

Methods: International observational study. All adult (> 16 years) patients in the ICON audit who had a urine output measurement on the day of admission were included. To investigate the association between oliguria and mortality, we used a multilevel analysis.

Results: Of the 8292 patients included, 2050 (24.7%) were oliguric during the first 24 h of admission. Patients with oliguria on admission who had at least one additional 24-h urine output recorded during their ICU stay ($n = 1349$) were divided into three groups: transient—oliguria resolved within 48 h after the admission day ($n = 390$ [28.9%]), prolonged—oliguria resolved > 48 h after the admission day ($n = 141$ [10.5%]), and permanent—oliguria persisting for the whole ICU stay or again present at the end of the ICU stay ($n = 818$ [60.6%]). ICU and hospital mortality rates were higher in patients with oliguria than in those without, except for patients with transient oliguria who had significantly lower mortality rates than non-oliguric patients. In multilevel analysis, the need for RRT was associated with a significantly higher risk of death (OR = 1.51 [95% CI 1.19–1.91], $p = 0.001$), but the presence of oliguria on admission was not (OR = 1.14 [95% CI 0.97–1.34], $p = 0.103$).

Conclusions: Oliguria is common in ICU patients and may have a relatively benign nature if only transient. The duration of oliguria and need for RRT are associated with worse outcome.

Keywords: Urine output, Renal replacement therapy, Mortality

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Introduction

Regardless of the exact criteria used to define it, oliguria is often observed in critically ill patients, and yet there are many questions regarding its clinical relevance and impact on outcomes. Reduced urine output can be a physiological response or a reflection of altered tissue perfusion or renal dysfunction [1–3].

Although urine output is now widely used as one of the criteria for the diagnosis and staging of acute renal failure [4–7], there are relatively few studies that have specifically assessed urine output or oliguria as a marker of acute renal failure or outcomes in general populations of intensive care unit (ICU) patients [2, 8, 9]. The clinical importance of oliguria likely depends on its duration. For example, a 1-h period of oliguria during an emergency admission is less important than if the symptom persists for longer periods, when it is more likely to reflect impaired renal function [10, 11].

To provide some global insight into the impact of oliguria and its persistence on outcomes in general ICU patients, we reviewed the large, international Intensive Care over Nations (ICON) database to evaluate the occurrence of oliguria and its association with the need for renal replacement therapy (RRT) and mortality.

Patients and methods

This study is a substudy of the ICON audit [12]. All adult (>16 years) patients admitted to a participating ICU (see the list in the “Acknowledgements”) between May 8 and May 18, 2012, were included in the audit, except those who stayed in the ICU for <24 h for routine postoperative surveillance. Participation was voluntary, with no financial incentive. Ethics committee approval was obtained by the participating institutions according to local ethical regulations.

Data were collected daily for a maximum of 28 days in the ICU and entered using electronic case report forms via a secured internet-based website. Survival data were collected at the time of ICU and hospital discharge, or at 60 days, whichever occurred first. Detailed instructions and definitions were available through a secured website for all participants before starting data collection and throughout the study period. Any additional queries were answered on a per case basis. Validity checks were made at the time of electronic data entry, including plausibility checks within each variable and between variables. Data were further reviewed by the coordinating center for completeness and plausibility, and any doubts clarified with the participating center. There was no on-site monitoring.

Data collection on admission included demographic data and comorbidities. Clinical and laboratory data for the SAPS II score [13] were reported as the worst values within the first 24 h after admission. A daily evaluation

of organ function was performed according to the Sequential Organ Failure Assessment (SOFA) score [5]; organ failure was defined as a SOFA subscore >2 for the organ in question. ICU interventions, including RRT and mechanical ventilation, were recorded daily.

Clinical and microbiologically proven infections were reported daily as well as antimicrobial therapy. Infection was defined according to the criteria of the International Sepsis Forum [14]. Sepsis was defined as the presence of infection with associated organ failure [15]. Septic shock was defined as sepsis associated with cardiovascular failure requiring vasopressor support (SOFA cardiovascular score ≥ 3). The presence of a decision to withhold/withdraw a life-sustaining measure at any time during the ICU stay was also recorded.

On the case report form, investigators recorded urine output in milliliters as a total for each 24-h period. On the day of admission, urine output data were recorded for the period from the time of admission till the start of the next ICU day. For the purposes of this study, oliguria was defined as a calculated urine output <0.5 ml/kg/h averaged over a 24-h period [2]. To calculate the urine output for the 24-h admission day period, if full urine output data for the first 24 h of admission were recorded, these data were used for the determination of oliguria “on admission.” If data were provided for only X hours on the day of admission (because, for example, the patient was admitted at 10 pm and 24-h urine measurement started at midnight so only 2-h urine output were noted), the estimation of urine output on admission was averaged from the data for the X hours and the data from the first full day on the ICU (2nd day 24-h urine output/ $24 \times [24 - X]$). If no data were recorded for the admission day, we were unable to estimate an admission urine output and the patient was not included. The methods of measuring urine output or of assessing body weight were not recorded. Patients with comorbid chronic renal failure were excluded.

For analysis of evolution during the ICU stay, we included only patients who had a urine output recorded on the day of admission and at least one other 24-h urine output value, and separated them into three groups:

- Transient oliguria—oliguria resolved within 48 h after the 24-h admission day
- Prolonged oliguria—oliguria resolved more than 48 h after the 24-h admission day and not present at the end of the ICU stay
- Permanent oliguria—oliguria present on the day of admission and persisting for the whole ICU stay or again present at the end of the ICU stay

Statistical analysis

Data are shown as means with standard deviation (SD) or 95% confidence intervals (CI), medians and interquartile ranges (IQR), numbers, and percentages. For the descriptive statistics, only available data were used so missing data were subtracted from the denominator when calculating percentages. Differences between groups in distribution of variables were assessed using the analysis of variance (ANOVA), Kruskal-Wallis test, Student's *t* test, Mann-Whitney test, chi-square test, or Fisher's exact test as appropriate.

Individual countries were classified into three income groups according to the 2011 gross national income (GNI) per capita, calculated using the World Bank Atlas method [16]: GNI < \$4035 = low and lower middle income, GNI \$4036–12,475 = upper middle income, and GNI > \$12,476 = high income.

To investigate the association between oliguria on admission and mortality, we used a three-level technique with the structure of an individual patient (level 1) admitted to a specific hospital (level 2) within a particular country (level 3). So patients were nested within hospitals within countries. The model includes hospital and country units as random effects to express the concept that patients from the same country and treated in the same hospital share a common environment. The dependency between patients in a hospital within a country is captured through the use of random intercepts. The explanatory variables considered in the model were:

- Individual-level factors: age, sex, SAPS II score, type of admission, source of admission, highest concentration of creatinine, daily fluid balance, mechanical ventilation or RRT at any time during the ICU stay, fluid balance, presence of recorded end-of-life decision, comorbidities, severity of sepsis during the ICU stay, oliguria on admission
- Hospital-level factors: type of hospital, ICU specialty, total number of ICU patients in the previous year, number of staffed ICU beds
- Country-level factors: GNI

Collinearity between variables was checked by inspection of the correlation between them, by looking at the correlation matrix of the estimated parameters, and by looking at the change in parameter estimates and at their estimated standard errors [17]. Q-Q plots were drawn to check for normality in the residuals. The results of fixed effects (measures of association) are given as odds ratios (OR) with their 95% CI. Random effects (measures of variation) measures included the variance (var) and its standard error (se). The restricted maximum likelihood (REML) procedure, which gives unbiased estimates of the model parameters, was used. The Wald test was used to assess

the significance of included covariates. The percentage of cases correctly classified and the area under the receiver operating characteristic curve (AUC) are given to quantify the discriminating power of the model. Missing cases for the included variables were analyzed using the missing-value indicator method.

Data were analyzed using IBM® SPSS® Statistics software, version 26 for Windows and R software, version 3.6.1 (CRAN project). All reported *p* values are two-sided, and a *p* value < 0.05 was considered to indicate statistical significance.

Results

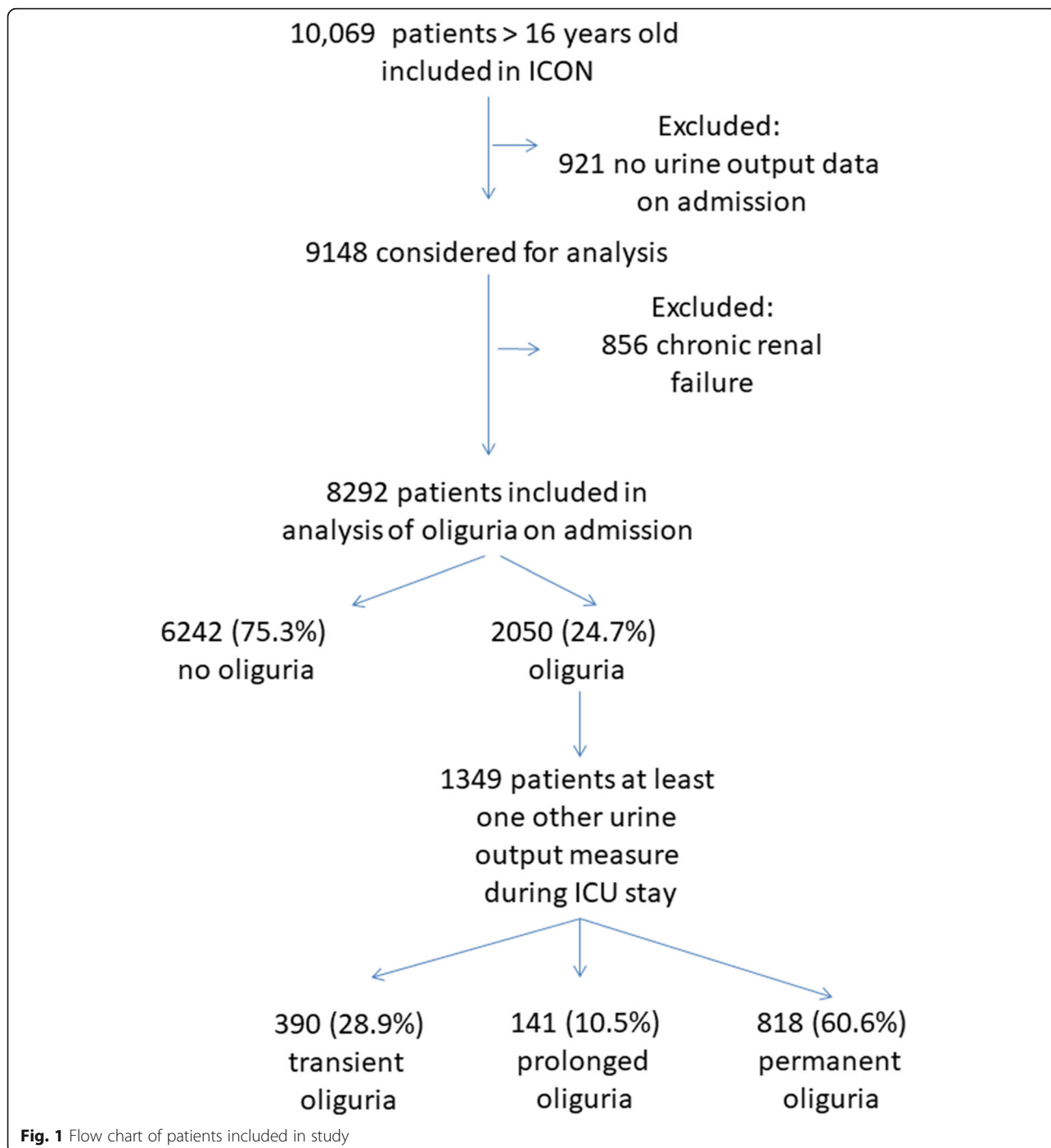
Of the 10,069 patients included in the ICON audit, 9148 had urine output data on the day of admission; 856 had comorbid chronic renal failure and were excluded, leaving 8292 patients for analysis (Fig. 1).

Patients with oliguria on admission

A total of 2050 (24.7%) patients had oliguria on the 24-h admission period, with a median urine output of 0.3 [IQR 0.1–0.4] ml/kg/h compared to 1.1 [IQR 0.8–1.6] ml/kg/h in patients who were not oliguric on admission ($p < 0.001$) (Table 1). Patients with oliguria on admission were older and more severely ill than those without, and a higher proportion had a medical diagnosis and comorbid heart failure, liver cirrhosis, and human immunodeficiency virus (HIV) infection (Table 1). They were more likely to have sepsis (24.5% vs 16.7%, $p < 0.001$) and to have all forms of organ failure, except hepatic (Table 1). Vasopressor use was higher in patients with oliguria at admission than in those without (36.9% vs 26.8%, $p < 0.001$).

ICU (26.8% vs 11.5%, $p < 0.001$) and hospital (34.5% vs 16.7%, $p < 0.001$) mortality rates were more than twice as high in patients with oliguria on admission than in those without (Table 1). End-of-life decisions were more common in oliguric patients than in the other patients (Table 2).

RRT was needed at some point during the ICU stay in 442 (21.6%) of the patients with and in 407 (6.5%) of the patients without oliguria on admission ($p < 0.001$) (Table 2). Multilevel analysis revealed that the need for RRT was associated with a statistically significant increased risk of death (OR = 1.51 [95% CI 1.19–1.91], $p = 0.001$), but the presence of oliguria on admission was not (OR = 1.14 [95% CI 0.97–1.34], $p = 0.103$) (Table 3). After controlling for patient and hospital factors and GNI, there was significant between-hospital (var = 0.5 [se = 0.09], $p < 0.001$) and between-country (var = 0.23 [se = 0.08], $p = 0.004$) variation in risks of in-hospital death (Table 3), indicating that the occurrence of in-hospital death was influenced by both hospital- and country-related factors.



Persistence of oliguria during ICU stay

A total of 1349 patients had at least one additional urine output measurement recorded during their ICU stay. Oliguria was transient in 390 (28.9%) of these patients, prolonged in 141 (10.5%), and permanent in 818 (60.6%) (Table 4). ICU mortality was 7.1% when oliguria was transient, significantly lower than in the patients without oliguria (11.5%, $p = 0.037$); rates were 10.9% when oliguria was prolonged and 28.9% when permanent (Table 4).

RRT was used in the ICU in 48 (12.3%), 63 (44.7%), and 273 (33.4%) patients with transient, prolonged, and permanent oliguria, respectively; 102 (19%) patients with permanent oliguria died in the ICU without receiving RRT. RRT was started within 24 h in 72.4% of patients with oliguria (75.0% vs 73.0% vs 71.8% in patients with transient, prolonged, and permanent oliguria, respectively). Among patients receiving RRT, ICU mortality was higher in non-oliguric patients than in those with

Table 1 Characteristics of the study cohort on admission to the ICU stratified according to whether or not oliguria was present

	All patients <i>n</i> = 8292	Oliguria at admission		<i>p</i> value
		No <i>n</i> = 6242 (75.3%)	Yes <i>n</i> = 2050 (24.7)	
Urine output (ml/kg/h) median [IQR]	0.9 [0.5–1.4]	1.1 [0.8–1.6]	0.3 [0.1–0.4]	< 0.001
Age, years, mean ± SD	59.2 ± 18.2	58.1 ± 18.3	62.5 ± 17.4	< 0.001
Male, <i>n</i> (%)	4928 (60.0)	3724 (60.2)	1204 (59.4)	0.55
Severity scores, mean ± SD				
SAPS II score	40.8 ± 17.5	37.9 ± 15.1	49.8 ± 20.8	< 0.001
SOFA score at admission	6.2 ± 4.2	5.7 ± 3.8	7.6 ± 5.0	< 0.001
SOFA score at admission (without renal subscore)	5.3 ± 3.7	5.1 ± 3.5	5.8 ± 4.2	< 0.001
Type of admission, <i>n</i> (%)				
Surgical (non-trauma)	2939 (37.2)	2374 (39.9)	565 (29.2)	< 0.001
Medical	4335 (54.9)	3063 (51.4)	1272 (65.7)	
Trauma	569 (7.2)	478 (8.0)	91 (4.7)	
Other	48 (.6)	40 (.7)	8 (.4)	
Source of admission, <i>n</i> (%)				
Other hospital	825 (9.9)	625 (10.0)	200 (9.8)	< 0.01
ER/ambulance	3151 (38.0)	2336 (37.4)	815 (39.8)	
OR/recovery room	1569 (18.9)	1304 (20.9)	265 (12.9)	
Hospital floor	2117 (25.5)	1529 (24.5)	588 (28.7)	
Other	630 (7.6)	448 (7.2)	182 (8.9)	
Comorbidities, <i>n</i> (%)				
COPD	1012 (12.2)	737 (11.8)	275 (13.4)	0.06
Cancer	891 (10.7)	684 (11.0)	207 (10.1)	0.29
Metastatic cancer	288 (3.5)	205 (3.3)	83 (4.0)	0.11
Hematologic cancer	178 (2.1)	126 (2.0)	52 (2.5)	0.16
Insulin	682 (8.2)	496 (7.9)	186 (9.1)	0.12
Heart failure, NYHA III/IV	648 (7.8)	445 (7.1)	203 (9.9)	< 0.001
HIV infection	56 (.7)	33 (.5)	23 (1.1)	< 0.01
Cirrhosis	283 (3.4)	188 (3.0)	95 (4.6)	< 0.001
Immunosuppression	259 (3.1)	184 (2.9)	75 (3.7)	0.11
Steroid therapy	273 (3.3)	208 (3.3)	65 (3.2)	0.78
Chemotherapy	239 (2.9)	181 (2.9)	58 (2.8)	0.94
Organ support, <i>n</i> (%)				
Mechanical ventilation	4227 (51.0)	3184 (51.0)	1043 (50.9)	0.92
Renal replacement therapy	321 (3.9)	97 (1.6)	224 (10.9)	< 0.001
Vasopressor use	2429 (29.3)	1672 (26.8)	757 (36.9)	< 0.001
Type of organ failure, <i>n</i> (%) (alone or in combination)				
Respiratory	1867 (22.5)	1334 (21.4)	533 (26.0)	< 0.001
Coagulation	530 (6.4)	345 (5.5)	185 (9.0)	< 0.001
Hepatic	885 (10.7)	658 (10.5)	227 (11.1)	0.51
CNS	1972 (23.8)	1435 (23.0)	537 (26.2)	< 0.01
Renal	1341 (16.2)	524 (8.4)	817 (39.9)	< 0.001
Cardiovascular	2296 (27.7)	1580 (25.3)	716 (34.9)	< 0.001

Table 1 Characteristics of the study cohort on admission to the ICU stratified according to whether or not oliguria was present (Continued)

	All patients n = 8292	Oliguria at admission		p value
		No n = 6242 (75.3%)	Yes n = 2050 (24.7)	
Number of organ failures, n (%)				
None	1771 (21.4)	1489 (23.9)	282 (13.8)	< 0.001
1 organ	2344 (28.3)	1805 (28.9)	539 (26.3)	
2 organs	1693 (20.4)	1302 (20.9)	391 (19.1)	
3 organs	1231 (14.8)	883 (14.1)	348 (17.0)	
> 3 organs	1253 (15.1)	763 (12.2)	490 (23.9)	
Sepsis, n (%)	1543 (18.6)	1041 (16.7)	502 (24.5)	< 0.001
ICU stay, median [IQR]	3.0 [2.0–6.0]	3.0 [2.0–6.0]	3.0 [1.0–7.0]	< 0.001
In survivors	3.0 [1.0–6.0]	3.0 [1.0–6.0]	3.0 [0.0–7.0]	0.046
In non-survivors	3.0 [0.0–8.0]	5.0 [1.0–10.0]	2.0 [0.0–6.0]	< 0.001
Hospital stay, median [IQR]	10.0 [5.0–20.0]	10.0 [6.0–20.0]	8.0 [2.0–18.0]	< 0.001
In survivors	11.0 [2.0–21.0]	11.0 [2.0–21.0]	11.0 [1.0–22.0]	0.075
In non-survivors	5.0 [0.0–14.0]	7.0 [1.0–15.0]	3.0 [0.0–10.0]	< 0.001
ICU mortality, n (%)	1234 (15.2)	700 (11.5)	534 (26.8)	< 0.001
Hospital mortality, n (%)	1649 (21.1)	983 (16.7)	666 (34.5)	< 0.001

SD standard deviation, SAPS II Simplified Acute Physiology Score II, SOFA Sequential Organ Failure Assessment, ER emergency room, OR operating room, COPD chronic obstructive pulmonary disease, NYHA New York Heart Association, HIV human immunodeficiency virus, CNS central nervous system, ICU intensive care unit, IQR interquartile range. Percentages are calculated after excluding missing data

transient or prolonged oliguria but lower than in those with permanent oliguria (Table 4). The maximum serum creatinine concentration was higher in patients with prolonged and permanent oliguria than in those with transient oliguria (Table 4). The mean daily fluid balance during the ICU stay was significantly higher in patients

with permanent oliguria than in those with transient or prolonged oliguria (Table 4).

Discussion

The present study in a large cohort of ICU patients with urine outputs measured on admission and during the

Table 2 Interventions and occurrence of sepsis during the ICU stay

	All patients n = 8292	Oliguria		p value
		No n = 6242 (75.3%)	Yes n = 2050 (24.7%)	
Creatinine, highest concentration (mg/dl), median [IQR]	1.0 [0.8–1.5]	0.9 [0.7–1.3]	1.3 [0.9–2.4]	< 0.001
Daily fluid balance ^a , ml, median [IQR]	81.0 [– 504.1–730.4]	3.3 [– 612–605.7]	356.3 [– 153.2–1116.7]	< 0.001
Mechanical ventilation, n (%)	4769 (57.5)	3579 (57.3)	1190 (58.0)	0.59
RRT, n (%)	849 (10.2)	407 (6.5)	442 (21.6)	< 0.001
Hemofiltration, n (%)	590 (7.1)	268 (4.3)	322 (15.7)	< 0.001
Hemodialysis, n (%)	551 (6.6)	266 (4.3)	285 (13.9)	< 0.001
Sepsis severity, n (%)				
No sepsis	5718 (69)	4403 (70.5)	1315 (64.1)	< 0.001
Sepsis	1104 (13.3)	858 (13.7)	246 (12.0)	
Shock	1470 (17.7)	981 (15.7)	489 (23.9)	
Decision to withhold/withdraw life-sustaining therapy, n (%)	1068 (12.9)	728 (11.7)	340 (16.6)	< 0.001

^aTotal fluid balance divided by the length of ICU stay. RRT renal replacement therapy

Table 3 Multilevel analysis of factors associated with hospital mortality

Variables	OR (95% CI)	p value
Fixed effects, varying within clusters		
Age	1.00 (1.00–1.01)	0.19
Sex, male	0.99 (0.85–1.14)	0.848
SAPS II	1.05 (1.05–1.06)	< 0.001
Type of admission (%)		
Surgical	Ref	na
Medical	1.53 (1.26–1.86)	< 0.001
Trauma	1.53 (1.14–2.05)	0.004
Other	1.92 (0.71–5.17)	0.196
Source of admission		
OR/recovery	Ref	na
Other hospital	1.17 (0.81–1.68)	0.404
ER/ambulance	1.12 (0.84–1.49)	0.458
Hospital floor	1.65 (1.26–2.16)	< 0.001
Other	1.20 (0.81–1.80)	0.366
Comorbidities		
COPD	0.98 (0.73–1.31)	0.877
Cancer	1.41 (1.15–1.74)	0.001
Metastatic cancer	1.20 (0.86–1.67)	0.281
Hematologic cancer	1.75 (1.25–2.44)	0.001
Insulin	0.84 (0.64–1.09)	0.189
Heart failure, NYHA III/IV	1.54 (1.19–1.99)	0.001
HIV infection	0.73 (0.27–1.94)	0.523
Cirrhosis	2.12 (1.45–3.10)	< 0.001
Immunosuppression	1.19 (0.78–1.79)	0.419
Steroid therapy	1.17 (0.74–1.84)	0.497
Chemotherapy	0.92 (0.55–1.53)	0.748
Creatinine, highest [mg/dl]	1.00 (0.97–1.02)	0.796
Daily fluid balance ^a [l]	1.37 (1.25–1.50)	< 0.001
Procedures during the ICU stay		
Mechanical ventilation	2.66 (2.12–3.34)	< 0.001
Renal replacement therapy	1.51 (1.19–1.91)	0.001
Severity of sepsis		
No sepsis	Ref	na
Sepsis without shock	0.98 (0.75–1.28)	0.887
Septic shock	1.55 (1.25–1.92)	< 0.001
End-of-life decision	11.82 (6.70–20.84)	< 0.001
Oliguria on admission	1.14 (0.97–1.34)	0.103
Fixed effects, constant within clusters		
Type of hospital		
University/academic	Ref	na
Non-university	1.16 (0.88–1.52)	0.293

Table 3 Multilevel analysis of factors associated with hospital mortality (Continued)

Variables	OR (95% CI)	p value
Number of patients admitted to the ICU (in 2011)		
750+	Ref	na
500–749	0.95 (0.76–1.19)	0.663
250–499	0.95 (0.68–1.31)	0.746
< 250	1.21 (0.77–1.91)	0.415
ICU specialty		
Surgical	Ref	na
Medical	0.63 (0.38–1.04)	0.072
Mixed	0.73 (0.54–1.00)	0.047
Others	0.94 (0.58–1.52)	0.79
Staffed ICU beds		
15+	Ref	na
< 15	1.12 (0.87–1.44)	0.397
Income		
High	Ref	na
Upper middle	1.81 (1.20–2.73)	0.005
Low and lower middle	2.05 (1.37–3.08)	0.001
Random effects		
Country		
Variance (se)	0.23 (0.08)	
p value	0.004	
Hospital within country		
Variance (se)	0.50 (0.09)	
p value	< 0.001	

^aTotal fluid balance divided by the length of ICU stay
 OR odds ratio, SAPS II Simplified Acute Physiology Score II, ER emergency room, OR operating room, COPD chronic obstructive pulmonary disease, NYHA New York Heart Association, HIV human immunodeficiency virus. The percentage of cases correctly classified with this model is 88.6%. The AUC is 91.5% (95% CI 90.7–92.3%)

ICU stay reveals that oliguria is present in about one fourth of critically ill patients on admission to the ICU. The presence of oliguria on admission was not independently associated with an increased risk of death, but the persistence of oliguria during the ICU stay was associated with higher ICU and hospital mortality rates.

There are relatively few published data on the frequency of oliguria in general ICU patients. Oliguria is frequently observed in the perioperative period and may be the consequence of hypovolemia and/or pain, both triggering the sympathetic nervous system, which in turn lead to activation of the renin-angiotensin-aldosterone system with ensuing oliguria. However, oliguria may also represent a warning of deteriorating renal function, especially in critically ill patients. Macedo et al. reported that 47% of their cohort of 317 surgical ICU patients had an episode of oliguria (urine output < 0.5 ml/kg/h for at least 6 consecutive

Table 4 Creatinine concentrations, fluid balance, renal replacement therapy, and mortality rates in patients with transient, prolonged, and permanent oliguria

	Non-oliguric on admission <i>n</i> = 6242	Oliguria during ICU stay, <i>n</i> = 1349			<i>p</i> value (across groups)
		Transient <i>n</i> = 390 (28.9%)	Prolonged <i>n</i> = 141 (10.5%)	Permanent <i>n</i> = 818 (60.6%)	
SAPS II score, mean ± SD	37.9 ± 15.1	47.1 ± 16.7 [‡]	54.4 ± 17* [‡]	49.7 ± 18.8 [‡]	< 0.001
Creatinine, highest concentration (mg/dl), median [IQR]	0.9 [0.7–1.3]	1.2 [0.8–2.1] [‡]	1.6 [1.1–3.4]* [‡]	1.5 [0.9–2.8]* [‡]	< 0.001
Daily fluid balance ^a , ml, median [IQR]	3.3 [–612–605.7]	49.9 [–521–650]	105.0 [–541.3–780.1]	308.9 [–171.5–1123.7]* [‡]	< 0.001
RRT at admission, <i>n</i> (%)	97 (1.6)	22 (5.6) [‡]	31 (22)* [‡]	121 (14.8)* [‡]	< 0.001
RRT during ICU stay, <i>n</i> (%)	407 (6.5)	48 (12.3) [‡]	63 (44.7)* [‡]	273 (33.4)* [‡]	< 0.001
ICU mortality, <i>n</i> (%)	700 (11.5)	27 (7.1) [‡]	15 (10.9)	232 (28.9)* [‡]	< 0.001
In non RRT patients, <i>n</i> (%)	580 (10.2)	22 (6.6)	8 (10.7)	102 (19.1)* [‡]	< 0.001
In RRT patients, <i>n</i> (%)	120 (29.9)	5 (10.9) [‡]	7 (11.3) [‡]	130 (48.3)* [‡]	< 0.001
End-of-life decision, <i>n</i> (%)	728 (11.7)	47 (12.1)	12 (8.5)	163 (19.9)* [‡]	< 0.001
In non RRT patients, <i>n</i> (%)	650 (11.1)	43 (12.6)	8 (10.3)	86 (15.8) [‡]	0.012
In RRT patients, <i>n</i> (%)	78 (19.2)	4 (8.3)	4 (6.3)	77 (28.2)* [‡]	< 0.001
Hospital mortality, <i>n</i> (%)	983 (16.7)	53 (14.7)	33 (24.8)*	296 (37.7)* [‡]	< 0.001

Pairwise *p* values: *vs transient; [‡]vs prolonged; [§]vs non-oliguric on admission. ^aTotal fluid balance divided by the length of ICU stay. IQR interquartile range, RRT renal replacement therapy, ICU intensive care unit. Percentages are calculated after excluding missing data

hours) during the ICU stay [1]. In an analysis of data from the FINNAKI study, as many as 92% of patients had an episode of oliguria as defined by a urine output < 0.5 ml/kg/h for a minimum of 0.5 h [3]. From their large database, Kellum et al. reported that 59% of ICU patients with acute kidney injury (AKI) met the KDIGO urine output criteria [8]. In a smaller cohort, Md Ralib et al. reported that 61% of patients with AKI met urine output criteria (< 0.5 ml/kg/h) [11], and in a study of critically ill cancer patients, 56% met urine output criteria for AKI [18].

The mortality rate was higher in patients with oliguria than in those without. In an analysis of 21,207 ICU patients from the large MIMIC-II database, Zhang et al. similarly reported increased mortality in patients with oliguria on day 1 [19]. However, oliguria may be an epiphenomenon of or surrogate for disease severity and after adjusting for multiple factors in the multilevel analysis, oliguria on admission was not independently associated with increased mortality in our patients. Importantly, we also analyzed the persistence of oliguria during the ICU stay and noted that ICU mortality rates in patients with transient oliguria were significantly lower than those in non-oliguric patients. Indeed, ICU and hospital mortality rates were lower in these patients with transient oliguria than in the overall ICON cohort (ICU 16.2%, hospital 22.4%, both *p* < 0.001) [12]. Our results therefore highlight that the duration of oliguria seems to be more important than the presence of oliguria per se. Macedo et al. similarly reported that prolonged duration of oliguria (> 12 h) was associated with increased mortality [1]. Vaara et al. [3] reported that 6–12 h of oliguria (0.3 to < 0.5 ml/kg/h), > 6

h of oliguria (0.1 to < 0.3 ml/kg/h), and severe oliguria (< 0.1 ml/kg/h) lasting > 3 h were independently associated with increased 90-day mortality. In an earlier analysis of the ICON database, patients who remained in stage 3 AKI (defined using the AKIN urine output or creatinine criteria) for a 7-day period had higher mortality rates than those in whom renal function recovered [20]. Prowle et al. [2] noted that although oliguria of longer than 1 h was significantly associated with the subsequent development of AKI diagnosed using creatinine criteria, short periods (1–6 h) of oliguria were not accurate at predicting AKI. In a cohort of patients undergoing major abdominal surgery, the presence of oliguria (urine output < 0.3 ml/kg/h) during surgery was indicative of an elevated probability of later AKI [21]. Similar results were recently published by Myles et al. [22] when a urine output < 0.5 ml/kg/h was used to define oliguria.

Our data also suggest that the increased mortality may be related more to the need for RRT than the oliguria itself, suggesting that other parameters, for example, high serum creatinine concentrations, may be better indicators for RRT than urine output. In an analysis of the MIMIC-II database, Mandelbaum et al. [9] reported that the increase in serum creatinine was a better predictor of the need for RRT than urine output, although urine output was a slightly better predictor of mortality. In their analysis, Kellum et al. reported that RRT use was more likely in patients diagnosed with AKI using urine output and creatinine concentration criteria than in patients diagnosed with AKI using just one of the two criteria [8]. We did not use the AKI criteria, preferring to

use the more global term of “acute renal failure” (defined by a renal SOFA score > 2) and need for RRT, because this puts the degree of renal impairment in relation to the dysfunction of the other organs. The SOFA criteria are actually more commonly used than AKI in the critical care literature [23]. Somewhat surprisingly, in the current analysis, RRT was used in only 33% of the patients with permanent oliguria; however, 66% of the patients with permanent oliguria who did not receive RRT were discharged to the hospital floor or another hospital and we have no information about ongoing patient management after ICU discharge. Patients with permanent oliguria were also more likely to have a recorded decision to withhold/withdraw a life-sustaining measure, possibly explaining why RRT was not used in some of these patients.

Recovery of a urine output is not itself a predictive factor, and urine output is not helpful in guiding fluid resuscitation [24]. Patients with permanent oliguria had a more positive fluid balance than those with transient or prolonged oliguria, which may explain in part the higher mortality rates in these patients, although it is not possible to determine whether these observations are epiphenomena or causal effects. Vaara et al. demonstrated an association between cumulative fluid overload (fluid accumulation > 10%) prior to RRT initiation and increased risk for 90-day mortality; the 90-day mortality rate of patients with fluid overload was 59.2% versus 31.4% without (difference of 27.8%, $p < 0.001$) [25]. In an earlier analysis of the ICON database, we reported that fluid balances became negative after the third ICU day in survivors but remained positive in non-survivors and that higher cumulative fluid balance at day 3 after ICU admission was independently associated with an increase in the hazard of death [26]. However, large randomized controlled trials have not shown a significant impact of fluid resuscitation strategy on clinical outcome or need for RRT [27].

Our study has several strengths but also some limitations. Strengths include the large database with patients from around the world, providing external validity, and the collection of data during the ICU stay. Limitations include the complexity of elements associated with oliguria that cannot be separated out, for example, we were unable to assess the need for fluids or diuretics or to assess the impact of different vasopressors. Moreover, criteria for RRT were not pre-defined due to the study design. Thus, RRT may have been used for fluid overload, increased urea and creatinine concentrations, electrolyte abnormalities, severe acidosis, and any combination of these. Another limitation is the lack of pre-admission data regarding the length of oliguria prior to ICU admission or the underlying reason for oliguria as well as the lack of post-discharge data. The methods of

monitoring urine output and assessing body weight also likely varied across centers and may have influenced the accuracy of measurements. Finally, we chose a definition of oliguria using a cut-off of urine output of 0.5 ml/kg/h, but this degree of urine output may in fact be adequate for some patients, e.g., the very obese and the very old.

Conclusion

In conclusion, the present study demonstrates that oliguria is a common occurrence in ICU patients, and suggests that it may have a relatively benign nature if only transient. For prognostic assessment, it is more the duration of oliguria and need for RRT than oliguria per se that are associated with a worse outcome.

Abbreviations

AKI: Acute kidney injury; GNI: Gross national income; ICU: Intensive care unit; KDIGO: Kidney Disease Improving Global Outcomes; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment

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Authors' contributions

JLV conceived and participated in the original study, collected and analyzed the data, drafted this manuscript, and approved the submitted version of the manuscript. AF participated in the original study, revised the manuscript for critical content, and approved the submitted version of the manuscript. PP participated in the original study, revised the manuscript for critical content, and approved the submitted version of the manuscript. SMJ participated in the original study, revised the manuscript for critical content, and approved the submitted version of the manuscript. UJ participated in the original study, revised the manuscript for critical content, and approved the submitted version of the manuscript. GAA participated in the original study,

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