

Laboratory diagnostic of acute kidney injury and its progression: Risk of underdiagnosis in female and elderly patients

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Introduction & Methods

Acute kidney injury (AKI)

Acute kidney injury is a common disease (incidence proportion 7.2 to 31.3%), with high morbidity and mortality rates (Table 1). Currently, AKI is defined and staged according to the KDIGO guidelines based on increased serum creatinine (SCr) and/or reduced urine volume (Table 2). It is known that serum creatinine (SCr) has limitations as a laboratory diagnostic parameter for AKI due to its dependence on muscle mass, which may lead to an incorrect or delayed diagnosis and staging for certain patient groups, such as women and the elderly. Especially AKI progression during hospitalization is strongly associated with adverse outcomes [3].

Stage	Serum Creatinine	Urine output
AKIN1*	1.5–1.9 times baseline OR ≥0.3 mg/dl (≥26.5 μmol/l) increase	<0.5 mL/kg/h for 6–12 h
AKIN2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
AKIN3*	3.0 times baseline OR increase in serum creatinine to ≥4.0 mg/dl (≥353.6 μmol/L) OR initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h

Table 2: Staging of AKI in adult patients according to KDIGO guidelines [2]. All stages can be reached by a relative SCr increases. Stages marked by * can additionally be reached by an absolute SCr criterion. AKI is defined as Increase in SCr by 0.3 mg/dl (26.5 μmol/l) within 48 hours or an increase in SCr to 1.5 times baseline within prior 7 days OR urine volume <0.5 mL/kg/h for 6 hours

Population	Age	Incidence (range)	RRT requirement (%)	Mortality (%)
Non-ICU hospitalized patients	Adult	<1 in 5 patients	<10	10–20
Critically ill patients	Adult	1 in 3 to 2 in 3 patients	5–11	NR
	Paediatric	1 in 4 patients (10–82%)	1–2	11
Patients undergoing cardiac surgery	Adult	1 in 5 patients (2–50%)	<5	10
	Paediatric	1 in 3 to 1 in 2 patients	NR	6
Patients with sepsis	Adult	1 in 20 to 1 in 2 patients	15	30–60

ICU, intensive care unit; NR, not reported; RRT, renal replacement therapy.

Table 1: Epidemiology and outcomes of AKI across cohorts [1].

Types of criteria for AKI detection and staging:

- 1) Increase in the last seven days by at least 1.5 times baseline.
- 2) Absolute increase in the last two days.
- 3) Creatinine limits exceeded (if also relative/absolute increase according to 1 or 2).

→ Especially criterion 2 should be more difficult to achieve in people with less muscle mass.

Cohort

Cases eligible for inclusion (final dataset) were used to create 3 final cohorts, which were analyzed in terms of general demographics, AKI stage distribution and AKI progression, stratified by age group and sex.

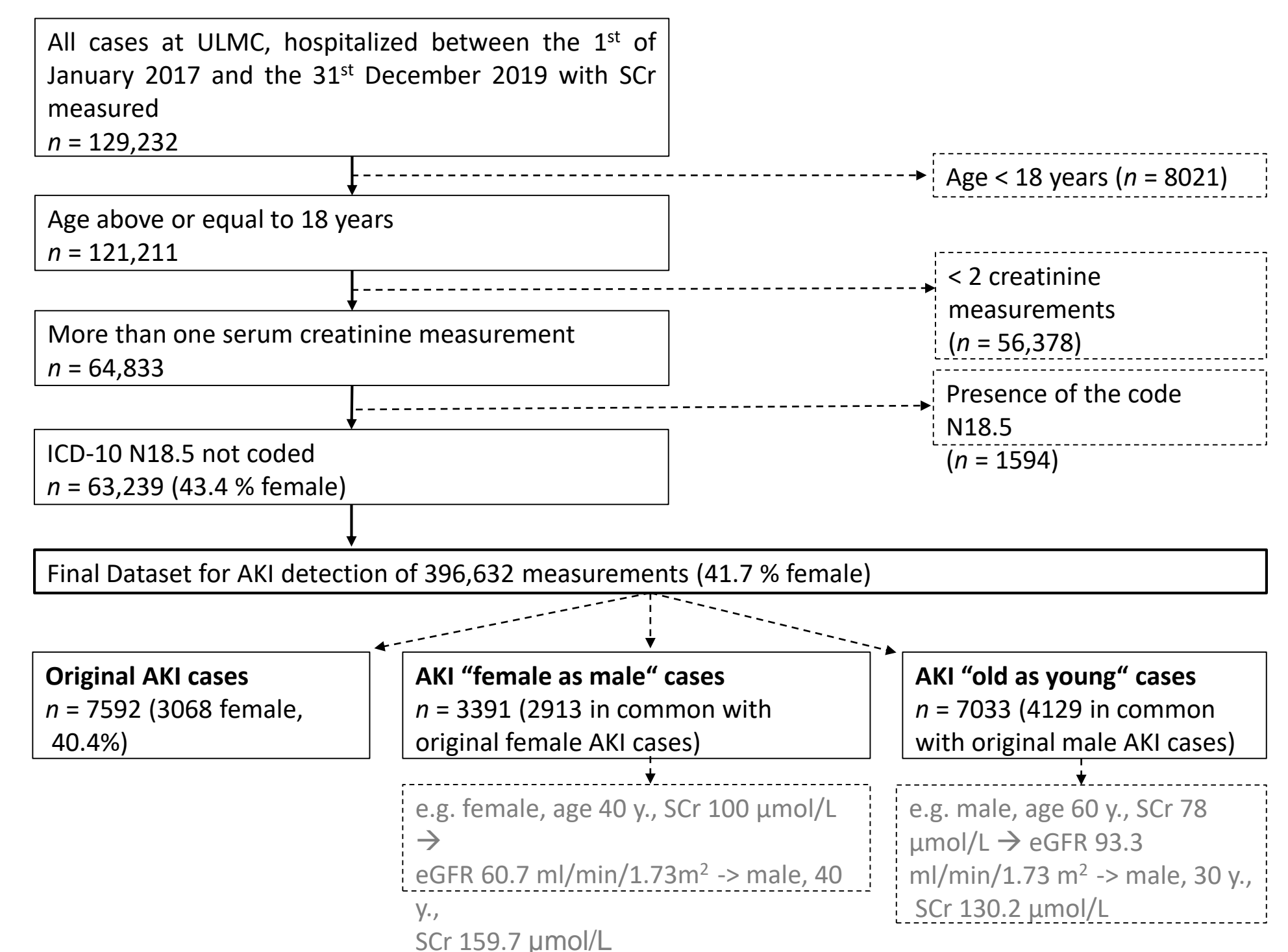


Figure 1: Refinement of data from the University of Leipzig Medical Centre (ULMC). Three final cohorts were established and analysed (bold).

Results

Characteristics of female and male AKI patients

AKI in females

- ↓ Incidence proportion
- ↓ Cases with progression
- ↓ eGFR at admission and discharge
- ↓ reaching AKIN3
- ↑ Age

	Female	Male	p-Value
N AKI, incidence prop. (%)	3068, 11.2	4524, 12.6	<0.001
N progressive AKI, incidence prop. (%)	554, 7.3	904, 11.9	0.039
Age (years)	72.0 [60.4–80.9]	67.7 [57.9–77.8]	<0.001
Total length of hospitalization (days)	16.2 [9.1–29.6]	17.6 [9.1–31.6]	0.038
First eGFR (mL/min/1.73 m ²)	59.9 [36–85.4]	63.4 [39.3–88.2]	<0.001
Last eGFR (mL/min/1.73 m ²)	53.2 [32.7–82.2]	55.9 [35.7–84.5]	<0.001
Time to first AKI (days)	4.7 [1.9–10.8]	4.5 [1.8–9.9]	0.073
Maximum AKI is AKIN3 (%)	12.3	16.6	<0.001
In-hospital mortality (%)	22.0	23.0	0.310

Table 3: Comparison of AKI cases in females and males. Continuous measures given as median [interquartile range]. Cohort: Original AKI cases.

By which criterion do females and males reach their AKI stage?

AKI in females

AKIN1 and AKIN3 mostly reached through relative criterion

Criteria	AKIN1, n, %			AKIN3, n, %		
	Female (n = 6011)	Male (n = 9365)	p-value	Female (n = 1032)	Male (n = 1984)	p-value
Absolute	1214, 20.2	2750, 29.4	<0.001	138, 13.4	302, 15.2	0.190
Both	1450, 24.1	2510, 26.8	<0.001	294, 28.5	936, 47.2	<0.001
Relative	3347, 55.7	4105, 43.8	<0.001	600, 58.1	746, 37.6	<0.001

Table 4: Comparison of fulfilled criteria in the detection of AKIN1 and AKIN3 for females and males according to KDIGO [2]. Multiple instances of AKI are considered per case. AKIN2 is detected exclusively via criterion 1, thus remains irrelevant for sex differences. Overall P (AKIN1) <0.001 (χ² test statistic = 235.6157226) and P(AKIN3) <0.001 (χ² test statistic = 123.9028779).

AKI in age groups

Recalculating AKI

Females as male ↑ maximum AKIN 3 reached
Old as young ↑ maximum AKIN3 reached

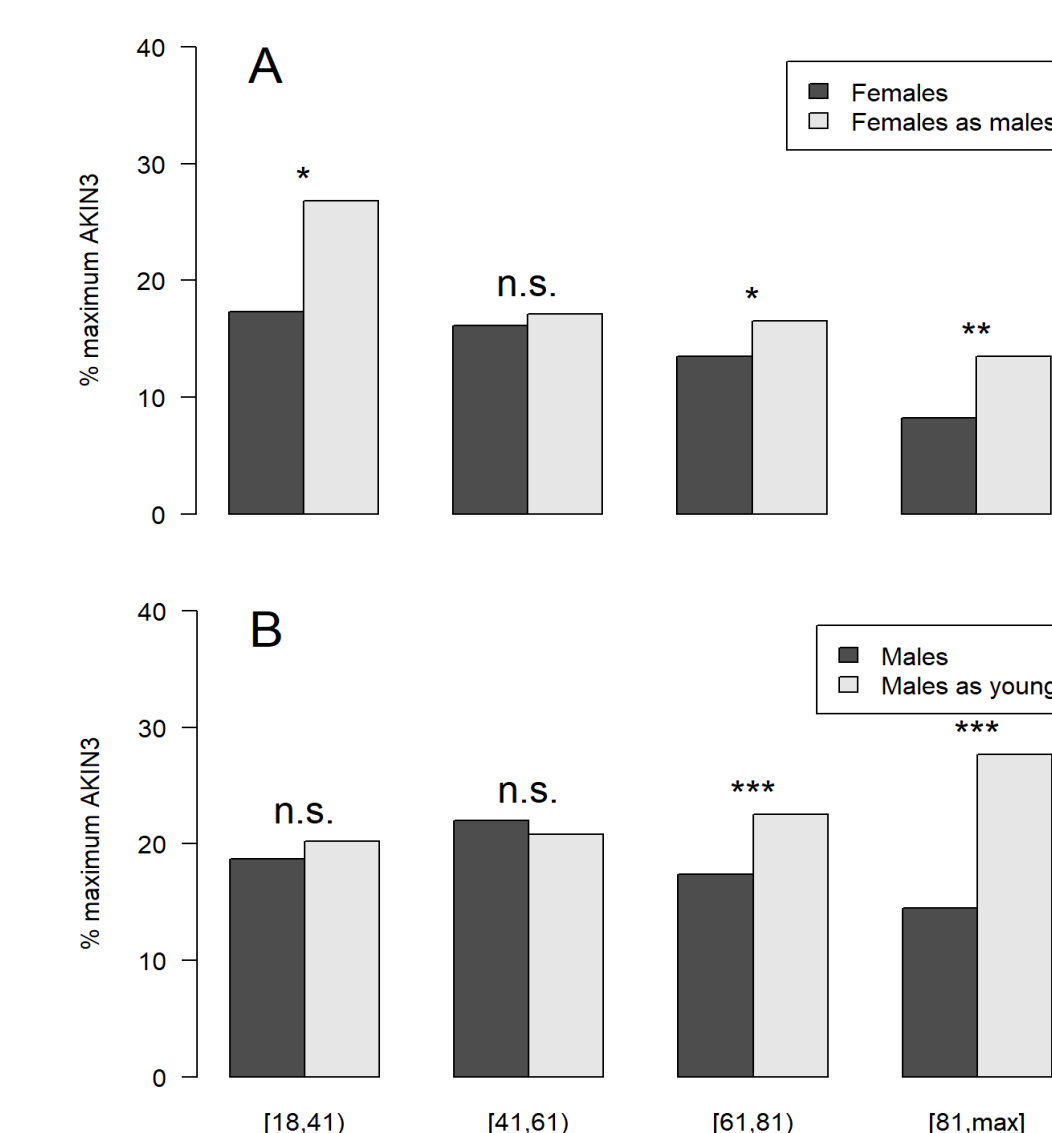


Figure 2: Proportion of AKI cases reaching AKIN3 during hospitalization per age group. Panel A compares females to the recalculated cohort females as males. Proportions decline with age group, but are consistently higher in the recalculated cohort. Panel B compares males to the recalculated cohort males as young. Differences in proportions increases with age.

Conclusion

- Current detection and staging of AKI likely harbors the risk for underdiagnosis in women and older individuals
- Exclusive consideration of SCr as a laboratory parameter and the use of static absolute criteria to define an AKI stage may result in a biased diagnosis
- Criteria for laboratory-based AKI diagnosis should be expanded to include
 - a factor that compensates for sex and age
 - measure of filtration that is unlikely to be influenced by sex, age or muscle mass in general

Supplement:

Recalculation SCr females as male:
Below/at sex-specific knot: $SCr = e^{\wedge} (\ln(eGFR/141/0.993^{\wedge} Age) / (-0.411)) * 0.9 * 88.42$
above sex-specific knot: $SCr = e^{\wedge} (\ln(eGFR/141/0.993^{\wedge} Age) / (-1.209)) * 0.9 * 88.42$
Recalculation SCr old as young:
Equations above with Age set to 30 years

References:

- [1] Hoste et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol 14, 607–625 (2018). <https://doi.org/10.1038/s41581-018-0052-0>
- [2] KDIGO. Clinical Practice Guideline for Acute Kidney Injury. Kidney Int. 2012, 2, 124–138.
- [3] Kister et al. Acute Kidney Injury and Its Progression in Hospitalized Patients—Results from a Retrospective Multicentre Cohort Study with a Digital Decision Support System. PLOS ONE 2021, 16 (7), e0254608. <https://doi.org/10.1371/journal.pone.0254608>.

Abbreviations:

ULMC - University Leipzig Medical Center
AKI - Acute kidney injury
SCr - Serum creatinine
eGFR - estimated glomerular filtration rate



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