ACUTE KIDNEY INJURY IN VERY OLD PATIENTS - INCIDENCE, SEVERITY, RISK FACTORS AND SHORT-TERM OUTCOMES

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Running head: Acute kidney injury in the very old

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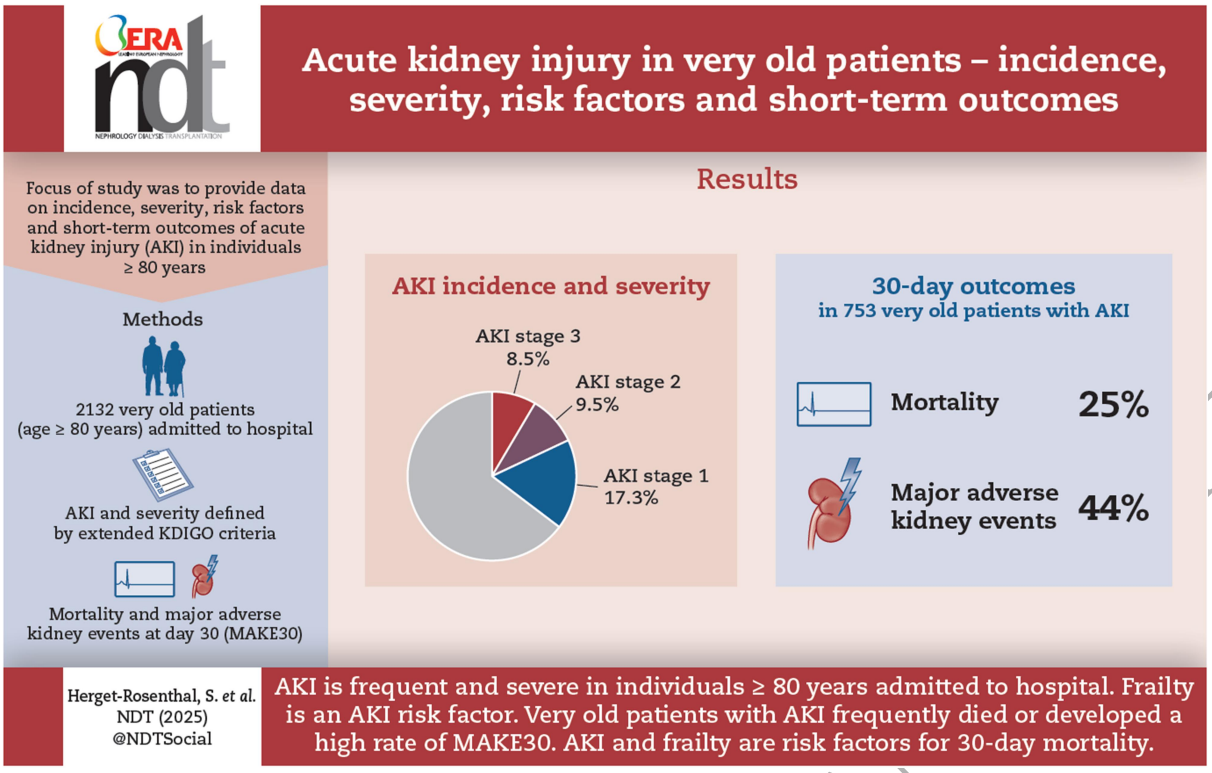
GRAPHICAL ABSTRACT



ABSTRACT

Background and hypothesis.

Although old age is a risk factor for acute kidney injury (AKI), data on AKI in individuals ≥80 years is limited. We aimed to provide data on AKI incidence, severity, and outcomes, to identify risk factors of AKI and 30-day mortality in those ≥80 years.

Methods.

Cohort study of 2132 patients admitted to hospital. AKI was defined and classified by extended KDIGO criteria to detect community-acquired AKI, frailty as a clinical frailty score ≥5. Primary endpoints were AKI and its stages, secondary endpoints 30-day mortality and major adverse kidney events (MAKE30), a composite of mortality, new renal replacement therapy, or serum creatinine values ≥200% of baseline, all at 30 days.

Results.

Median age was 86 years. AKI was frequent (35.3%) and predominately community-acquired (80.2%). The incidence rate of AKI rose with increasing age, reaching the maximum in patients 95 years old. 48.9% of AKI patients developed stage 1, while 27.0% and 24.1% reached stages 2 and 3, respectively. Frailty was identified as an independent AKI risk factor (adjusted odds ratio (aOR) 2.42 (95% confidence intervals (CI) 1.93–3.03). 30-day mortality rate was significantly higher in AKI compared to non-AKI patients (25.4 vs. 7.6%), 44.4% of AKI patients developed MAKE30. Among others, AKI and frailty were risk factors for 30-day mortality (aOR 3.02 (95% CI 2.25-4.07) and 1.53 (95% CI 1.16-2.02)), with frailty exceeding AKI in patients ≥90 years.

Conclusions.

AKI occurs frequently, increases with age, is severe and predominately community-acquired in individuals ≥80 years admitted to hospital. Frailty is a risk factor for AKI besides established factors. Very old patients with AKI more frequently died or developed a high rate of the composite endpoint MAKE30. AKI and frailty are risk factors for 30-day mortality. The effect of frailty on mortality exceeded that of AKI in nonagenarians.

Keywords: acute kidney injury, epidemiology, frailty, very old

KEY LEARNING POINTS

What was known:

- Very old age is a risk factor for acute kidney injury (AKI)
- Data on incidence, severity and outcome of AKI in individuals ≥ 80 years is limited

This study adds:

- AKI is frequent, severe and predominately community-acquired in individuals ≥ 80 years admitted to hospital. In contrast to individuals ≥ 80 years, AKI in individuals 65-79 years is less frequent but of even higher severity and predominately hospital acquired
- Frailty, acute heart failure and dehydration are risk factors for AKI in the very old
- Patients ≥ 80 years with AKI frequently have persistent renal dysfunction, new renal replacement therapy or are deceased on day 30 after hospital admission

Potential impact:

- Attention should be paid to frailty and fluid status to prevent AKI in patients ≥ 80 years
- Interventions to prevent AKI in the very old should be implemented in out-patient care by general practitioners

INTRODUCTION

Old age has been associated with particularly high acute kidney injury (AKI) rates and identified as a risk factor for AKI [1-3]. Functional and structural renal changes in combination with the high prevalence of diabetes, hypertension and chronic kidney disease (CKD) reduce the ability to compensate for renal injuries and cause excessive vulnerability to development of AKI in the old [4-6]. Increased life expectancy has resulted in a continuous, disproportionate and rapid growth in the population of 80 years and above worldwide. This age group is presently considered very old (VOP) [7, 8]. However, data on AKI in VOP is limited, as these patients were usually subsumed under patients at an age of 65-79 years [9]. In addition, most studies on AKI in VOP were small, and none applied the recently extended AKI definitions (eKDIGO) which improve the detection of community-acquired AKI (CAAKI). The latter may have caused underestimation of AKI frequency [9-11]. Meta-analysis reported high rates of AKI in VOP, and identified CKD, hypertension and chronic heart failure as risk and renin-angiotensin-system inhibitors as protective factors [9]. Modifiable risk factors and outcome of AKI have not been analyzed in this age group. As no therapy for AKI currently exists, it is crucial to recognize and correct modifiable risk factors early to prevent AKI and to reduce the rate and severity of AKI as recently demonstrated [1, 12, 13]. Thus, it may be of particular interest to study the epidemiology of AKI in VOP to identify risk factors, and its impact on AKI specific morbidity and mortality.

Frailty is a multifactorial and complex syndrome, characterized by increased vulnerability and inability to cope with acute stressors, resulting from accelerated aging [14, 15]. Age and the prevalence of frailty increase in parallel [16]. Frailty has been shown to be an important predictor of poor prognosis in VOP in numerous acute diseases such as

myocardial infarction, stroke and acute heart failure [17-21]. However, there is a paucity of data on the impact of frailty on AKI in VOP [22-24].

We aimed (1) to provide data on AKI incidence, severity, and outcomes, (2) to identify risk factors, (3) to determine whether frailty affects AKI, and (4) to identify predictors of 30-day mortality, all in VOP.

MATERIALS AND METHODS

Patients, variables and outcome

This is a cohort study of VOP including a comparator cohort of patients aged 65 to 79 years, termed old patients (OP), both admitted to the Rotes Kreuz Krankenhaus, Bremen between January and December 2018. The Rotes Kreuz Krankenhaus is a secondary level hospital serving as a tertiary referral centre for cardiology, nephrology, trauma and vascular surgery. Patients were required to have ≥ 2 serum creatinine measurements during the hospital stay. We applied STROBE methodology (Fig. 1) [25]. Patients referred from other hospitals were not eligible due to potential information bias. We excluded patients with CKD stage G5, renal transplantation, intrinsic nephropathies such as renal vasculitis, rapid progressive glomerulonephritis, acute interstitial nephritis, and thrombotic microangiopathy, defined as proteinuria > 0.5 g/d and respective pathologic blood, urine and/or histology tests, elective admission < 48 hours, and patients with decisions to withhold life-sustaining treatment made on admission (Fig. 1, Supplementary tab. 1). Data was collected from electronic hospital and primary care physician's records. Baseline values were from data recorded on hospital admission, serum creatinine and estimated glomerular filtration rate (eGFR) pre-admission were values from 8 to 89 days before. Creatinine was measured with an enzymatic colorimetric assay and eGFR was calculated applying the creatinine-based European Kidney Function Consortium equation [26]. Clinical frailty score (CFS) was retrospectively assessed, a valid diagnostic method to estimate frailty in VOP admitted to hospital [14, 27].

Primary outcomes were AKI and its severity as defined and classified by the eKDIGO criteria in VOP [1, 10, 11]. AKI definition was (1) an increase or decrease in serum creatinine, either by ≥ 0.3 mg/dl in 48 hours or ≥ 50% within 7 days from admission, and/or (2) a decline or incline of urine output < 0.5 ml/kg/h, both for at least 6 hours.

CAAKI was classified according to eKDIGO as AKI starting pre-admission and recovering after admission, the remaining as hospital-acquired AKI (definitions are provided in supplementary table 1 [10, 11]. Daily urine volume data was available for 2065 patients (55.9 %). Secondary endpoints were mortality and major adverse kidney events (MAKE30), both on day 30 after hospital admission. MAKE30 is a composite of (1) serum creatinine increase ≥ 200 % compared to the lowest value prior or during hospital admission termed persistent renal dysfunction, (2) new renal replacement therapy, and/or (3) mortality, all at 30 days after admission. MAKE30 has become a generally acknowledged and specific measure of short-term AKI outcome [28-31]. Additionally, we multiplied age (in years) by the CFS as a proxy variable representing the combination of biological and pathological aging. We performed sensitivity analyses comparing VOP with CAAKI and without AKI as well as frail VOP with and without AKI, the later to detect components of frailty possibly associated with AKI. Further definitions of variables are presented in the supplementary table 1.

Statistical analysis

Data was complete for most variables and missing data was indicated. Continuous variables were expressed as means ± SD or median (25^{th} - 75^{th} percentile) and compared using paired Student's t - or Wilcoxon-test [(1)] as appropriate. Categorical variables were expressed as total counts and percentages, and compared with Chi^2 [(2)], Fisher's exact or Cochran-Armitage for trend [(3)] tests. We constructed multivariable, logistic regression models with AKI, CAAKI, frail patients with AKI, and mortality by day 30 as dependent variables, including all potentially associated risk factors with $P < 0.10$ in bivariate analyses. Additionally, we constructed these models entering all biological plausible variables without checking for significance. All models were assessed using Hosmer-Lemeshow test and C-statistic. Receiver operating characteristic curves were generated to

compare the ability of age, CFS, and the product of age and CFS to discriminate patients with AKI from those without. Differences between AUROCs were compared by the DeLong method [4]. Two-sided $P < 0.05$ was considered to be statistically significant. Strength of association was classified as strong (odds ratio (OR) ≥ 3.0), moderate (OR 1.86 – 2.99) or weak (OR ≤ 1.85) [32]. No correction for multiple testing was applied, as this is an exploratory analysis. Results should be interpreted accordingly.

RESULTS

We studied 2132 VOP with a median age of 86 years (83; 89) and compared them to 1563 OP. AKI was frequent in VOP (35.3 %) and predominately community-acquired (80.2 %). AKI patients 80 years and above were older, more frequently male and frail, and were characterized by higher rates of emergency admissions, higher sequential organ failure assessment scores, reduced renal function as shown by serum creatinine and eGFR prior to and on admission as well as CKD, other chronic comorbidities and most AKI risk factors, such as acute heart failure and dehydration (Tab. 1). In 41.9 % AKI in VOP was acute-on-chronic kidney disease. VOP with and without AKI did not differ in respect to the distribution of subgroups acute heart failure and dehydration. In the subgroup of VOP with CAAKI, the differences in regard to fraily, dementia, and dehydration were more pronounced, while especially the frequencies of acute heart failure, intraarterial iodinated radiographic contrast, sepsis and shock were less marked in comparison VOP without AKI (Supplementary tab. 2). As demonstrated in Figure 2, the incidence rate of AKI in VOP rose with increasing age, reaching the maximum in patients 95 years old. In VOP with AKI, serum creatinine markedly increased to its maximum value, while it changed negligibly in non-AKI VOP. The majority of VOP with AKI developed stage 1, while approximately one quarter each reached maximum stages 2 and 3 (Fig. 3). Seventy-seven patients (10.2 %) were treated with RRT. VOP receiving RRT were younger, less frail, and were especially characterized by higher frequencies of CKD, acute severe morbidity prior to AKI development, hospital-acquired AKI and MAKE30 compared to VOP with AKI but without RRT (Supplementary tab. 3). Approximately in half of these patients RRT was initiated within the first 24 hours after admission. Compared to OP with AKI, AKI in VOP was more frequent, less severe, more commonly community-acquired, and associated with more chronic and less acute morbidity (Tab. 1).

We identified frailty as moderately strong, acute heart failure and dehydration as strong risk factors of AKI. This was independent of sepsis and shock, the strongest AKI risk factors in our analysis, and other factors such as CKD and intraarterial iodinated radiographic contrast (Tab. 2). Parallel to progressive, pre-admission CKD, AKI frequency and severity of AKI increased (Supplementary tab. 4). In the subgroup analysis, renal function at baseline was more impaired in frail patients with AKI compared to all AKI patients (Supplementary tab. 5). Of note, frail patients with and without AKI had higher rates of chronic comorbidities and similar rates of acute comorbidities while the distributions between these conditions did not substantially differ when analyzing the entire cohort or frail patients exclusively. All principal independent risk factors of AKI which were identified in the complete cohort were also detected in the sensitivity analyses of VOP with CAAKI and frailty (Table 3). Nephrotoxic drugs aside from non-steroidal anti-inflammatory drugs were additionally identified as risk factors in CAAKI, and rhabdomyolysis and dementia in frail VOP. All models had high predictive power, were well fitted and left little room for variables not included in the model to explain AKI (Tab. 2 and 3). The models entering all biological plausible variables identified identical risk factors with similar strength of association (data not shown). Comparing age, CFS and the product of age and CFS, the latter performed best in discriminating VOP with from those without AKI. The product of age and CFS had an AUROC of 0.72 (95% confidence intervals (CI) 0.70 – 0.74) ($P < 0.001$ vs. age and CFS respectively [(4)]), age of 0.57 (95% CI 0.55 – 0.59) and CFS of 0.68 (95% CI 0.66 – 0.70) (Fig. 4).

Thirty days after hospital admission, median serum creatinine had markedly decreased in VOP with AKI to 1.60 mg/dl (1.20; 2.40) but still differed significantly from baseline values, similar to eGFR (33 ml/min/1.73 m^2 (25; 42); both $P < 0.001$ compared to baseline values [(1)]). In VOP without AKI, serum creatinine (0.90 mg/dl (0.80; 1.00); $P = 0.46$ [(1)]) and eGFR (52 ml/min/1.73 m^2 (46; 59); $P = 0.71$ [(1)]) on day 30 did not differ from

baseline values. Mortality rate on day 30 was substantially higher in AKI compared to non-AKI patients (26.0 vs. 7.6 %; risk ratio 3.42 (2.74 – 4.26); P < 0.001 [(2)]). More than two-fifths of VOP with AKI developed MAKE30 (Fig. 5). Total MAKE30 was primarily determined by high rates of its components persistent renal dysfunction and mortality on day 30 after hospital admission. In difference to OP, VOP with AKI had higher rates of MAKE30 and mortality on day 30 (Tab. 1). Comparing patients with maximum AKI stages 1, 2 and 3, the rates of MAKE30 (21.5 %, 57.1 %, and 87.9 %; P < 0.001 [(3)]), and of its components persistent renal dysfunction (2.2 %, 33.5 %, and 75.8 %; P < 0.001 [(3)]), new RRT (0 %, 0 %, and 19.7 %; P < 0.001 [(3)]) and mortality (19.8 %, 31.5 %, and 45.6 %; P < 0.001 [(3)]) increased progressively and parallel to AKI severity.

AKI was identified as a strong risk factor, frailty, and acute heart failure as weak risk factors for 30-day mortality, independently of established risk factors such as sepsis, shock, and chronic heart failure (Tab. 3). When dividing the entire cohort of VOP into age quartiles and adjusting for gender, diabetes, ischaemic heart disease, cerebrovascular disease, CKD, dementia, emergency admission, sepsis, shock, acute and chronic heart failure, the effect of AKI on 30-day mortality was strongest in the lowest age quartile with a continuous decrease with increasing age quartiles (Fig. 6). In contrast, frailty was not significantly associated with 30-day mortality in the lowest age quartile. However, its effect progressively increased in higher age quartiles, surpassing AKI in the highest age quartile.

DISCUSSION

Firstly, our data indicates that AKI occurs frequently, is severe and predominately community-acquired in patients 80 years and above admitted to hospital. In contrast to individuals ≥ 80 years, AKI in individuals 65-79 years is less frequent but of even higher severity and predominately hospital acquired in this study. Secondly, the likelihood of developing AKI markedly increased with age in VOP and almost doubled when comparing patients of 80 to those ≥ 95 years. Thirdly, we identified frailty, dehydration, and acute heart failure as moderate to strong risk factors of AKI in VOP. This was independent of sepsis and shock, the strongest AKI risk factors, and others. Of note, the product of age and CFS, a proxy variable constructed to incorporate both biological and pathological aging, was superior to its components when discriminating between old patients with and without AKI. Fourthly, VOP with AKI developed a high rate of the composite renal endpoint MAKE30 which was primarily determined by high rates of persistent renal dysfunction and mortality. Fifthly, AKI and frailty were independent risk factors associated with 30-day mortality in VOP. While the effect of AKI on 30-day mortality declined as age increased, the effect of frailty increased and exceeded that of AKI in nonagenarians.

AKI in VOP observed in this study was more frequent and severe than in previous studies as summarized in a recent meta-analysis [9]. Our older and frequently critically ill patients, predominately non-electively admitted to our hospital with specialities associated with higher AKI rates, more data on urine output, and the use of extended AKI criteria may account for this [9-11]. Lack of some urine volume data may underestimate the rate of AKI in our study [33]. The extended criteria more comprehensively capture CAAKI and increase the AKI rate. Although the increasing likelihood of developing AKI with age has previously been demonstrated, this is a novel finding in the age group significantly exceeding 80 years [34, 35]. The increase of AKI frequency with age is biologically

plausible. Vulnerability to developing AKI in the old is expected to increase as GFR and the ability to compensate for renal injuries decline with every additional year of life [4-6].

Our data on MAKE30 can only be compared to studies in younger patients and more selective cohorts [28-31, 36-40]. Both the rates of total MAKE30 and its components of mortality and new RRT were higher while persistent renal dysfunction rate was lower in the cohorts of younger, critically ill patients compared to our results [28, 29, 36-38]. In contrast, in the non-critically ill, the rates of MAKE30 and of all components were lower [30, 31, 39, 40]. These differences and the position of our results between those of critically and non-critically ill younger patients may be explained by approximately one quarter of critically ill patients in our cohort, the intermediate severity of acute illness, the high rates of CKD and other chronic comorbidities, and age. Higher CKD rates and age are likely to lower the capability of renal regeneration and increase persistent renal dysfunction after AKI. This combined with frequent frailty and severe chronic comorbidities may have also led to greater reluctance to offer RRT to our cohort.

Our findings extend the growing body of evidence. Frailty negatively impacts morbidity and mortality in numerous acute conditions [17-21]. To our knowledge, this is the first publication which has characterized frailty as an independent risk factor for AKI, and of mortality after AKI. Associations of frailty with both consecutive AKI and subsequent mortality have been described before but cohorts were small, predominately younger than 80 years, and frailty was not adjusted for other risk factors [23, 24]. Possibly, joint pathophysiological mechanisms such as increased proinflammatory response may explain the strong association of AKI and frailty in VOP. However, the underlying mechanisms still need to be deciphered and our analyses could not identify any component associated with frailty which led to increased AKI [15]. The higher prediction of AKI by means of the product of age and CFS, compared to the separate components suggests that biological and pathological aging may reciprocally potentiate the susceptibility to AKI in VOP [4-6].

The identification of AKI as a strong risk factor of 30-day mortality corresponds well with previous data [1, 41]. Of note, frailty may supersede this effect of AKI with increasing age which underscores the impact of frailty on negative outcome and indicates that biological and pathological aging in combination may potentiate their adverse effects. Although hypothetical, starting at a very old age frailty may become the most dominant factor determining mortality. Larger cohort are required to analyse the interaction of frailty and AKI on mortality more exactly.

In contrast to frailty, dehydration and acute heart failure are not novel as modifiable AKI risk factors. Simplified and to a limited extent they may be considered as the opposite ends of fluid balance. The identification of both as risk factors emphasizes that very old, comorbid patients may be particular vulnerable to hypo- and hypervolaemia [42-45]. To possibly prevent AKI and to lower the rate of AKI and its outcomes in VOP, particular attention should be paid to frailty, dehydration and acute heart failure in the bundle of AKI care. Although cumbersome, time consuming and in part protracted, measures to prevent, treat and correct these risk factors have been described [44-47]. As our data suggests that AKI in VOP is primarily community-associated, these interventions should be implemented in out-patient care predominately by general practitioners. Although we did not identify renin-angiotensin-inhibitors as protective factors of AKI, possibly due to their very frequent administration in VOP with and without AKI, these drugs may be especially valuable in preventing AKI in VOP [9, 44, 45]. This may presumably also apply to sodium-glucose transport protein 2 inhibitors [48]. However, our data was too limited to contribute to this issue.

One strength of our study is its large patient cohort with a typical cross-section of VOP. We optimized internal validity, potential confounding and bias by restricting it to the patients of interest, exact and valid definitions, comprehensive search, inclusion and identical measurements of variables and outcomes, complete data, and correcting for

differences by multivariate regression. The sensitivity analyses of CAAKI and frail patients with similar results to the complete cohort made our findings more robust. Its single-center and observational design may limit generalizability. Thus, our results require validation in larger multicenter studies and remain hypothesis generating. The extended AKI definition and severity classification which we applied are still novel and therefore requires more vigorous validation. However, this definition and classification may be clinically relevant, as our data suggests that both are associated with increased short-term morbidity and mortality of AKI which is consistent with the strong evidence for the previous definition and classification of AKI [1].

Although it is a well-established time period for acute medical conditions such as AKI, the 30-day follow-up may have biased findings towards the null as outcomes in VOP with and without AKI may have continued to diverge thereafter [28-31]. A further limitation is the focus on patients with emergency admission to hospital. However, AKI is more likely to occur and to be detected in hospitalized VOP and they require large medical and economic resources [1, 15]. Hence, it seemed plausible and worthwhile to study these patients in particular.

In conclusion, our study indicates that AKI is frequent, severe and occurs predominately in patients 80 years and above admitted to hospital. Frailty was identified as an independent risk factor of AKI, and VOP with AKI frequently developed short term outcomes such as 30-day mortality.

DATA AVAILABILITY STATEMENT

The dataset of this study is available from the corresponding author upon request.

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AUTHORS' CONTRIBUTIONS

SHR and AK designed the study, wrote the protocol and submitted the protocol for ethical approval. KS, KA and HF collected the data. SHR, MS and AK supervised the study and wrote the first draft. All authors analyzed the data, reviewed and edited the manuscript and approved the final version.

CONFLICT OF INTEREST STATEMENT

The authors have declared that no conflict of interest exists.

ETHICAL STANDARDS, APPROVAL AND CONSENT

All procedures in this study are in accordance with the 1964 Helsinki declaration and its later amendments. The study protocol was approved by the local ethics committee

(Medical Council Bremen, HR/RE-450). The requirement of obtaining informed consent to participate was waived by the local ethics committee because of the observational study design and as patient data were anonymised.

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Table 1. Patients' characteristics, acute and chronic conditions, and values prior to and on hospital admission

Variables	Age ≥ 80 years			Age 65 – 79 years			
	AKI [1] (N = 753)	Non-AKI [2] (N = 1379)	P 1 vs 2	AKI [3] (N = 429)	Non-AKI [4] (N = 1134)	P 3 vs 4	P 1 vs 3
Age (years)	86 (84; 90)	85 (82; 88)	< 0.001	71 (68; 75)	72 (68; 77)	0.01	< 0.001
Male gender, N (%)	325 (43.2)	483 (35.0)	< 0.001	248 (57.8)	599 (52.0)	0.08	< 0.001
Cerebrovascular disease, N (%)	203 (27.0)	296 (21.3)	0.004	27 (6.0)	45 (4.0)	0.05	< 0.001
Chronic heart failure, N (%)	361 (47.9)	479 (34.7)	< 0.001	124 (28.9)	285 (25.1)	0.13	< 0.001
Chronic kidney disease, N (%)	314 (41.7)	213 (15.4)	< 0.001	98 (22.8)	147 (13.0)	< 0.001	< 0.001
Dementia, N (%)	182 (24.3)	294 (21.3)	0.13	20 (4.7)	55 (4.9)	0.88	< 0.001
Diabetes, N (%)	299 (39.7)	353 (25.6)	< 0.001	130 (30.3)	270 (23.8)	0.009	0.001
Frailty, N (%)	387 (51.4)	391 (28.4)	< 0.001	60 (14.0)	125 (11.0)	0.11	< 0.001
Hypertension, N (%)	588 (78.1)	978 (70.9)	< 0.001	193 (45.0)	461 (40.7)	0.12	< 0.001
Ischaemic heart disease, N (%)	297 (39.4)	359 (26.0)	< 0.001	108 (25.2)	246 (21.7)	0.14	< 0.001
Renin-angiotensin-inhibitor, N (%)	351 (46.6)	731 (53.0)	0.006	269 (62.7)	762 (67.2)	0.07	< 0.001
SGLT-2- inhibitor, N (%)	2 (0.3)	9 (0.7)	0.35	4 (0.9)	21 (0.9)	0.26	0.20
Serum creatinine pre-admission (mg/dl)	1.10 (1.00; 1.10)	0.90 (0.80; 0.90)	< 0.001	1.07 (0.94; 1.27)	1.00 (0.89; 1.19)	< 0.001	0.17
Estimated GFR pre-admission (ml/min/1.73 m^2)	47 (41; 53)	54 (49; 60)	< 0.001	57 (51; 64)	60 (55; 66)	< 0.001	< 0.001
Emergency admission, N (%)	605 (80.3)	966 (70.1)	< 0.001	312 (72.7)	676 (59.6)	< 0.001	0.003
Primary diagnosis on admission, N (%)			0.23			0.51	0.17
Infectious	139 (18.5)	141 (10.2)		39 (9.1)	77 (6.8)		
cardiac	175 (23.2)	240 (17.4)		116 (27.1)	257 (22.7)		
respiratory	14 (1.9)	45 (3.3)		25 (5.8)	94 (8.7)		
malignancy/haematological	31 (4.1)	48 (3.5)		34 (7.9)	168 (14.8)		
vascular	78 (10.4)	144 (10.4)		59 (13.8)	85 (7.5)		
trauma	93 (12.3)	259 (18.8)		40 (9.4)	81 (7.1)		
rheumatological/orthopaedic	39 (5.2)	195 (14.1)		8 (1.9)	139 (12.3)		
gastrointestinal / liver	87 (11.5)	159 (11.5)		46 (10.7)	88 (7.8)		
renal	61 (8.1)	66 (4.8)		55 (12.9)	118 (10.4)		
neurological	24 (3.2)	59 (4.3)		0 (0)	0 (0)		
metabolic/endocrinological	12 (1.6)	18 (1.3)		6 (1.4)	22 (1.9)		
others	0 (0)	5 (0.4)		0 (0)	0 (0)		
SOFA score	5 (4.5; 5)	4 (3; 4)	< 0.001	6 (5; 7)	5 (4; 6)	< 0.001	< 0.001
SOFA score without renal category	4 (3; 4.5)	3 (3; 4)	< 0.001	5 (4.5; 6)	5 (4; 5)	0.29	< 0.001
Serum creatinine on admission (mg/dl)	1.40 (1.00; 1.90)	0.90 (0.80; 1.00)	< 0.001	1.30 (1.10; 1.80)	1.00 (0.90; 1.10)	< 0.001	0.17

Serum creatinine maximum (mg/dl)	2.20 (1.70; 3.00)	0.90 (0.80; 1.10)	< 0.001	2.70 (2.20; 3.60)	1.10 (1.00; 1.30)	< 0.001	< 0.001
Acute heart failure, N (%)	295 (39.2)	221 (16.0)	< 0.001	196 (45.7)	202 (17.8)	< 0.001	0.03
• ADHF, N (%)	94 (31.9)	60 (27.2)	0.35	18 (9.2)	9 (4.5)	0.01	0.003
• acute coronary syndrome, N (%)	65 (22.0)	47 (21.3)		72 (36.7)	51 (25.2)		
• arrhythmia, N (%)	21 (7.1)	25 (11.3)		16 (8.2	20 (9.9)		
• hypertensive crisis, N (%)	15 (5.1)	11 (5.0)		13 (6.6)	24 (11.9)		
• fluid overload, N (%)	28 (9.5)	16 (7.2)		4 (2.0)	7 (3.5)		
• mechanical cause, N (%)	23 (7.8)	19 (8.6)		20 (10.2)	16 (7.9)		
• pulmonary oedema, N (%)	6 (2.0)	7 (3.1)		9 (4.6)	21 (10.4)		
• endocarditis, N (%)	2 (0.7)	1 (0.5)		6 (3.1)	5 (2.5)		
• combination, N (%)	41 (13.9)	35 (15.8)		38 (19.4)	49 (24.3)		
Acute obstructive nephropathy, N (%)	42 (5.6)	25 (1.8)	< 0.001	2 (0.5)	1 (0.1)	0.18	< 0.001
Dehydration, N (%)	290 (38.5) (76.2/3.8/20.0/0/0) vs (85.1/1.1/11.7/2.1/0) *	129 (9.4) (74.4/6.2/16.3/3.1/0) vs (67.8/0.9/15.2/8.6/7.5) *	< 0.001	46 (10.7) (84.8/2.2/13.0/0/0) vs (93.5/0/6.5/0/0) *	15 (1.3) (86.7/0/13.3/0/0) vs (75.2/0/16.7/1.1/7.0) *	< 0.001	< 0.001
• urinary loss, N (%)	141 (48.6)	55 (42.6)	0.26	3 (6.5)	1 (6.7)	0.82	< 0.001
• gastrointestinal loss, N (%)	45 (15.5)	18 (14.0)		13 (28.3)	4 (26.6)		
• skin loss, N (%)	56 (19.3)	24 (18.6)		11 (23.9)	3 (20.0)		
• combination, N (%)	48 (16.6)	32 (24.8)		19 (41.3)	7 (46.7)		
Intraarterial iodinated radiographic contrast, N (%)	106 (14.1)	75 (5.4)	< 0.001	88 (20.5)	121 (10.7)	< 0.001	0.004
Non-steroidal anti-inflammatory drug, N (%)	126 (16.7)	235 (17.0)	0.86	10 (2.3)	20 (1.8)	0.54	0.17
Other nephrotoxic drugs, N (%)	31 (4.1)	23 (1.7)	< 0.001	8 (1.9)	11 (1.0)	0.19	0.02
Rhabdomyolysis, N (%)	58 (7.7)	12 (0.9)	< 0.001	37 (8.6)	7 (0.6)	< 0.001	0.58
Sepsis, N (%)	161 (21.4)	44 (3.2)	< 0.001	104 (24.2)	66 (5.8)	< 0.001	0.26
Shock, N (%)	124 (16.5)	55 (4.0)	< 0.001	89 (20.7)	70 (6.2)	< 0.001	0.07
CAAKI, N (%)	604 (80.2)			150 (35.0)			< 0.001
AKI stage 1, N (%) (CAAKI - N)	368 (48.9) (312)			121 (28.2) (89)			< 0.001
Stage 2, N (%) (CAAKI - N)	203 (27.0) (155)			220 (51.3) (34)			
Stage 3, N (%) (CAAKI - N)	182 (24.1) (137)			88 (20.5) (27)			
RRT, N (%)	70 (9.3)			61 (14.2)			0.01
MAKE30, N (%)	334 (44.4)			162/407 (39.8)			0.13
Mortality on day 30, N (%)	196 (26.0)			48/407 (11.8)			< 0.001
WLST, N (%) (DNI-DNR/RRT/full)	171 (22.7) (62/14/95)			37 (8.6) (25/2/10)			< 0.001

* Percentages of patients with dehydration versus no dehydration assessed by (1) ultrasound, (2) clinically (axillary dryness), (3) combination of (1) and (2), (4) other clinical tests, and (5) none.

ADHF - acutely decompensated chronic heart failure. AKI – acute kidney injury. CAAKI – community-acquired acute kidney injury. DNI-DNR – do not intubate and resuscitate. GFR – glomerular filtration rate. MAKE30 – major adverse kidney event on day 30. RRT – renal replacement therapy. SGLT-2 - Sodium-glucose-transport-protein-2. SOFA - sequential organ failure assessment. WLST – withdrawal of life-sustaining therapy.

Table 2. Multivariable logistic regression analysis of variables potentially associated with acute kidney injury in very old patients

Variables	Odds ratio	95 % Confidence intervals	P
Male gender	1.35	1.08 – 1.70	0.009
Cerebrovascular disease	1.24	0.94 – 1.58	0.11
Chronic heart failure	1.04	0.82 – 1.31	0.77
Chronic kidney disease	2.96	2.31 – 3.79	< 0.001
Diabetes	1.39	1.02 – 1.73	0.008
Frailty	2.42	1.93 – 3.03	< 0.001
Hypertension	1.22	0.97 – 1.55	0.09
Ischaemic heart disease	1.08	0.87 – 1.42	0.56
Renin-angiotensin-inhibitor	0.81	0.64 – 1.03	0.08
Emergency admission	0.85	0.65 – 1.11	0.23
Acute heart failure	3.94	3.40 – 5.66	< 0.001
Acute obstructive nephropathy	1.82	0.97 – 3.42	0.06
Dehydration	3.76	2.83 – 4.99	< 0.001
Intraarterial iodinated radiographic contrast	2.17	1.47 – 3.21	< 0.001
Other nephrotoxic drugs	1.82	0.92 – 3.58	0.09
Rhabdomyolysis	1.87	0.89 – 4.17	0.12
Sepsis	6.97	4.59 – 10.57	< 0.001
Shock	3.57	2.34 – 5.46	< 0.001

Homer-Lemeshow test X^2 = 9.51, P = 0.31; AUROC 0.83 (0.82 – 0.85).

Table 3. Multivariable logistic regression analyses of variables potentially associated with community-acquired acute kidney injury (CAAKI) and in frail patients, both in cohorts of very old patients

Variables	Analysis of CAAKI			Analysis of frail patients		
	Odds ratio	95 % Confidence intervals	P	Odds ratio	95 % Confidence intervals	P
Male gender	1.29	1.01 – 1.64	0.04	1.22	0.85 – 1.77	0.29
Cerebrovascular disease	1.29	0.97 – 1.71	0.08	-	-	-
Chronic heart failure	1.20	0.93 – 1.54	0.17	1.07	0.74 – 1.55	0.73
Chronic kidney disease	3.05	2.36 – 3.95	< 0.001	3.07	2.06 – 4.57	< 0.001
Dementia	1.17	0.88 – 1.56	0.27	1.73	1.18 – 2.53	0.005
Diabetes	1.55	1.20 – 1.99	0.008	1.20	0.82 – 1.76	0.34
Frailty	2.60	1.85 – 3.63	< 0.001	NA	NA	NA
Hypertension	1.47	1.10 – 1.98	0.01	1.05	0.70 – 1.59	0.80
Ischaemic heart disease	1.06	0.82 – 1.37	0.67	1.22	0.81 – 1.82	0.33
Renin-angiotensin-inhibitor	0.79	0.61 – 1.02	0.07	-	-	-
Emergency admission	0.95	0.71 – 1.29	0.71	-	-	-
Acute heart failure	4.14	3.15 – 5.45	< 0.001	4.18	2.71 – 6.43	< 0.001
Acute obstructive nephropathy	1.56	0.79 – 3.09	0.21	1.34	0.46 – 3.92	0.59
Dehydration	4.29	3.18 – 5.77	< 0.001	4.51	2.82 – 6.44	< 0.001
Intraarterial iodinated radiographic contrast	-	-	-	2.75	1.42 – 5.34	0.003
Other nephrotoxic drugs	2.37	1.19 – 4.72	0.01	1.93	0.73 – 5.06	0.18
Rhabdomyolysis	2.18	0.99 – 4.76	0.05	5.35	1.14 – 25.20	0.03
Sepsis	5.95	3.86 – 9.13	< 0.001	7.44	3.65 – 15.18	< 0.001
Shock	3.30	2.10 – 5.19	< 0.001	3.63	1.77 – 7.44	< 0.001

Analysis of CAAKI: Homer-Lemeshow test $X^2 = 4.25$, P = 0.83; AUROC 0.82 (0.81 – 0.84). Analysis of frail patients: Homer-Lemeshow test $X^2 = 11.48$, P = 0.18; AUROC 0.84 (0.81 – 0.87).

Table 4. Multivariable logistic regression analysis of variables potentially associated with mortality by day 30 after hospital admission in very old patients

Variables	Odds ratio	95 % Confidence intervals	P
Male gender	1.26	0.96 – 1.64	0.09
Cerebrovascular disease	1.29	0.95 – 1.74	0.10
Chronic heart failure	1.45	1.11 – 1.90	0.007
Chronic kidney disease	1.09	0.83 – 1.44	0.59
Dementia	1.22	0.90 – 1.66	0.21
Diabetes	1.08	0.81 – 1.42	0.61
Frailty	1.53	1.16 – 2.02	0.003
Ischaemic heart disease	0.93	0.70 – 1.24	0.63
Emergency admission	0.91	0.65 – 1.27	0.57
Acute heart failure	1.50	1.10 – 2.03	0.01
Acute kidney injury	3.02	2.25 – 4.07	< 0.001
Sepsis	1.96	1.35 – 2.85	< 0.001
Shock	2.28	1.56 – 3.31	< 0.001

Homer-Lemeshow test $X^2 = 4.16$, P = 0.84; AUROC 0.76 (0.74 – 0.78).

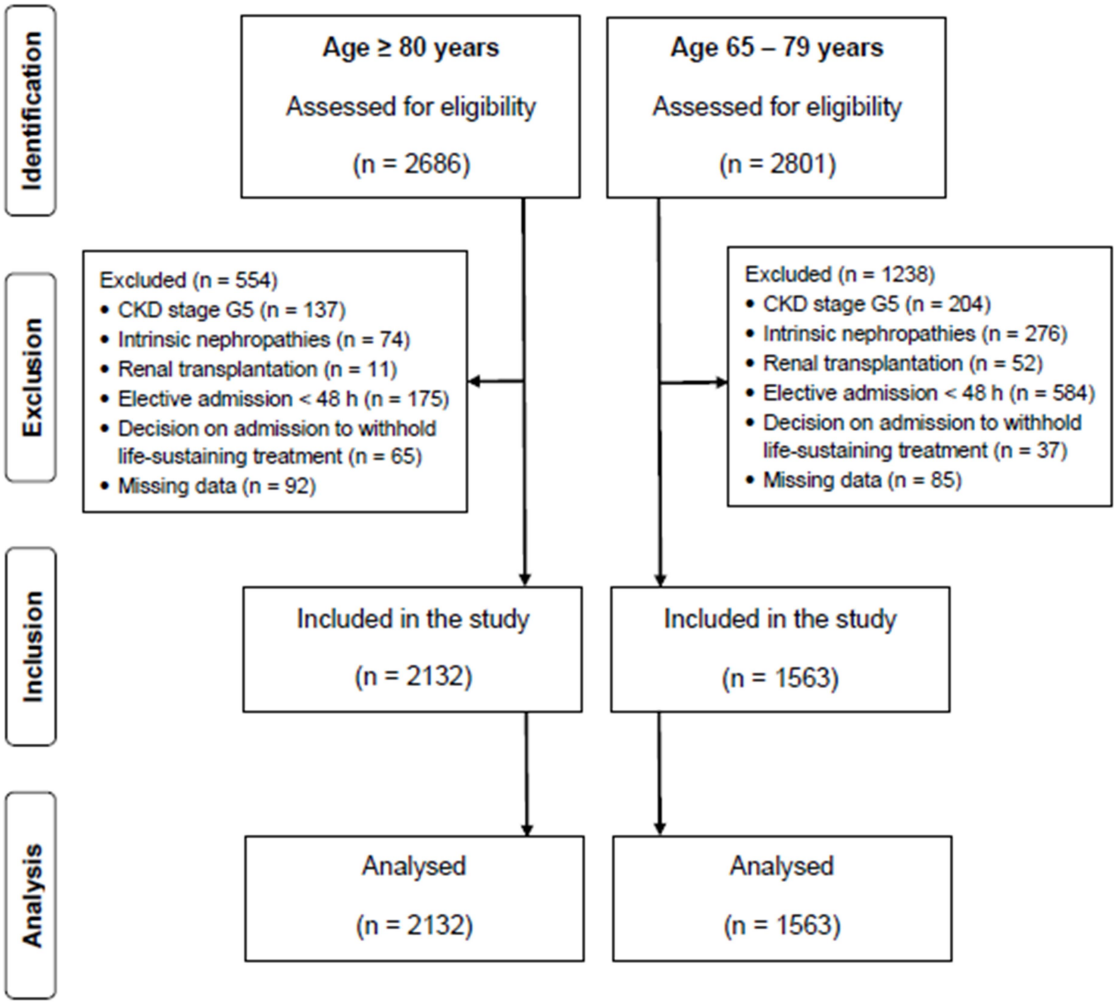

Figure 1. Flow diagram of the study participants.

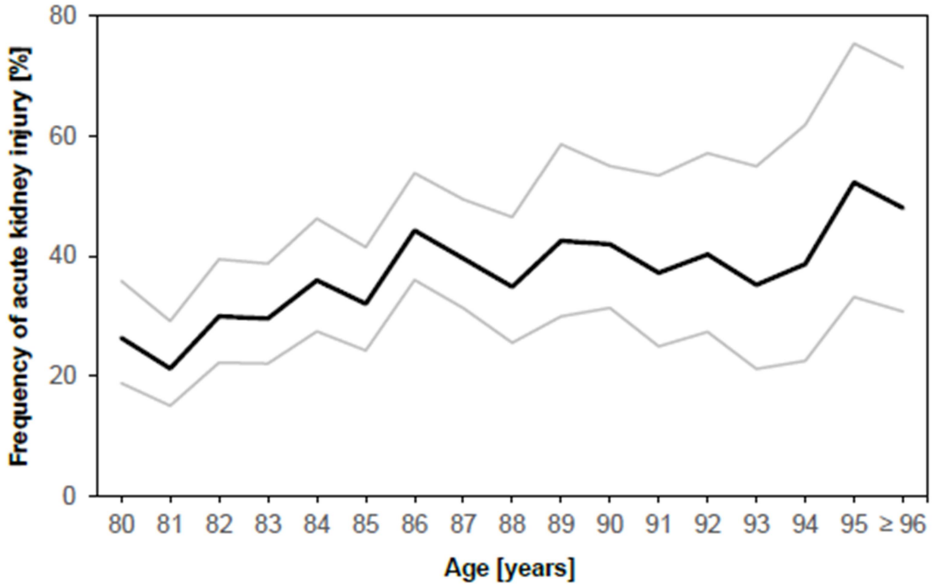

Figure 2. Frequency of acute kidney injury in very old patients per year of age. Data is presented as percentages. The grey lines indicate the 95% confidence intervals.

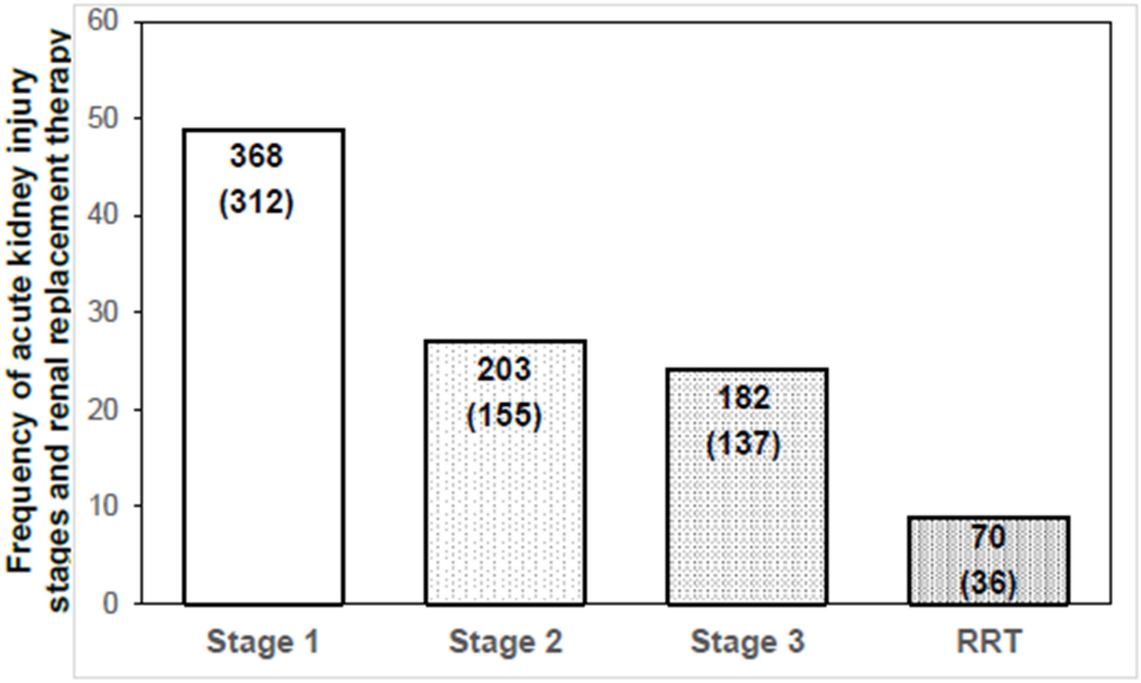

Figure 3. Frequency of maximum acute kidney injury (AKI) stages and new renal replacement therapy (RRT) in very old patients with AKI. Data is presented as percentages and total patient numbers (numbers of patients with community-associated AKI in parenthesis) in the columns.

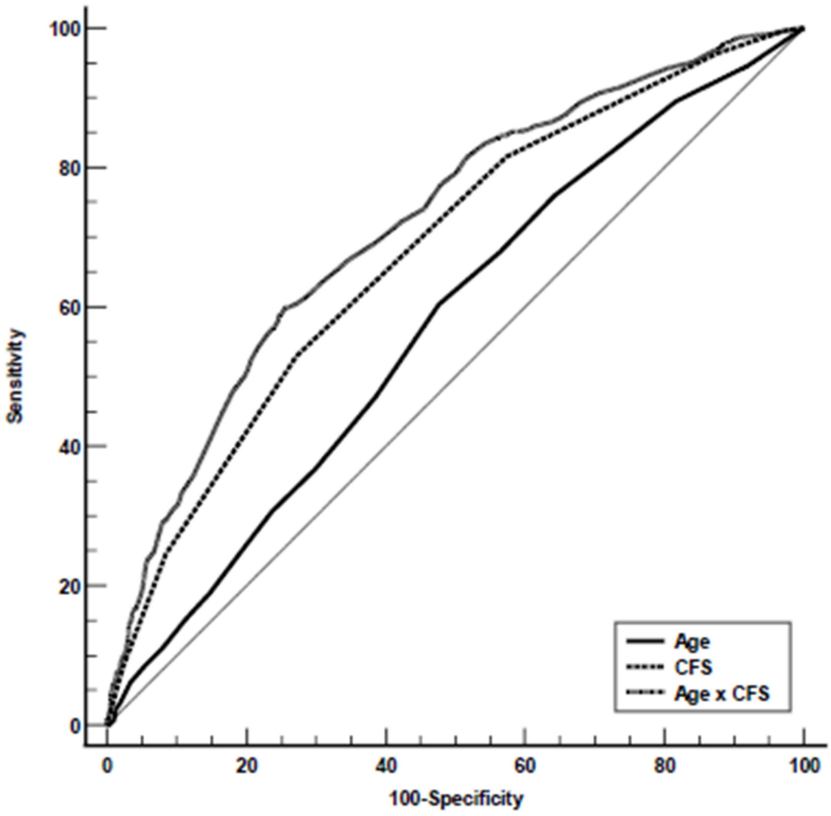

Figure 4. Comparison of the ability of age, clinical frailty score (CFS), and the product of age and CFS (age x CFS) to predict subsequent AKI by receiver operating characteristic curves.

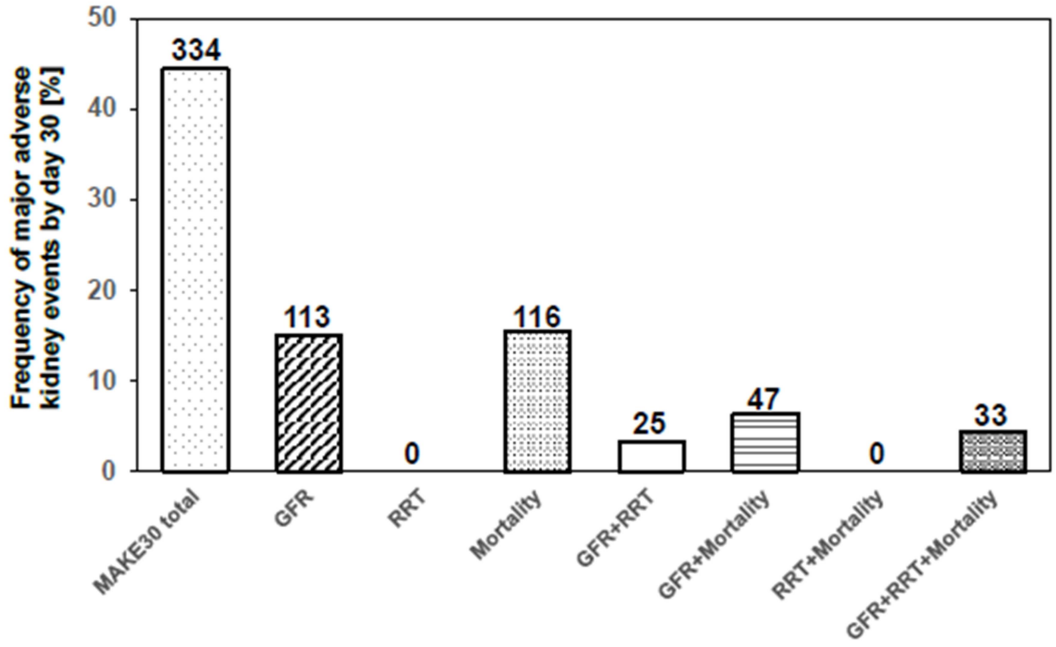

Figure 5. Frequency of any major adverse kidney event (MAKE30 total), persistent renal dysfunction (GFR), new renal replacement therapy (RRT), mortality, and their combinations, all in very old patients with acute kidney injury on day 30 after hospital admission. Data is presented as percentages and total patient numbers above the columns.

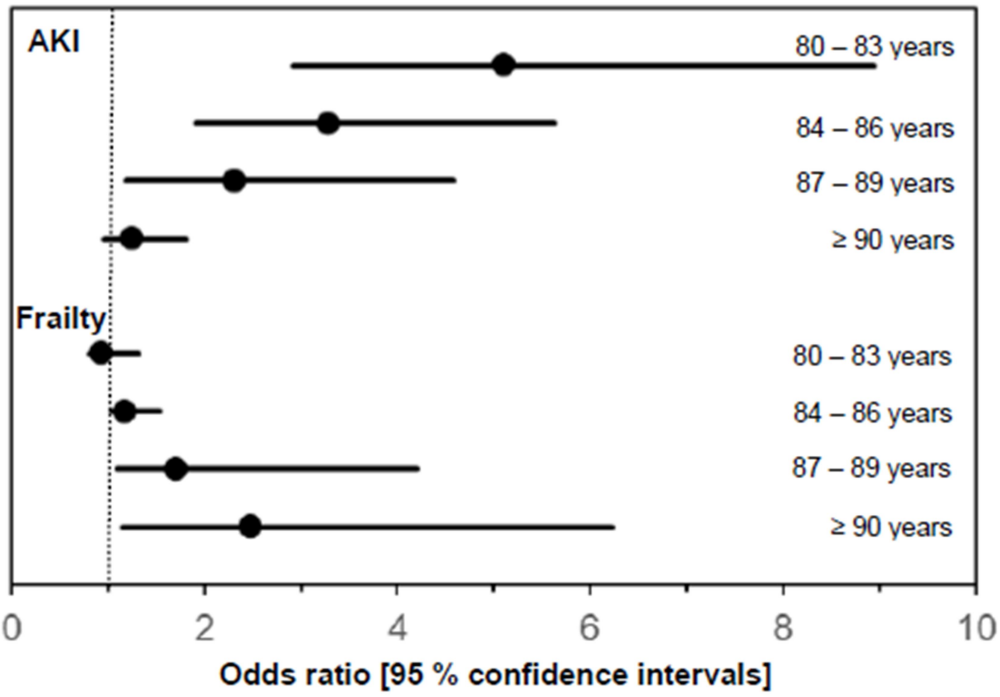

Figure 6. Association between acute kidney injury (AKI) and frailty, and 30-day mortality risk stratified by age quartiles in very old patients. Adjusted odds ratios of AKI and frailty are presented with 95% confidence intervals.