DR MIIKKA NIITTYVUOPIO (Orcid ID : 0000-0001-6060-1789)
PROFESSOR VILLE PETTILÄ (Orcid ID : 0000-0002-3921-4423)
DR JANNE HENRIK LIISANANTTI (Orcid ID : 0000-0002-5580-3447)

Article type : Clinical investigation

CAUSES OF DEATH FOR INTENSIVE CARE SURVIVORS WITH AND WITHOUT ACUTE KIDNEY INJURY IN FIVE-YEAR FOLLOW-UP

Running head: Causes of death for intensive care survivors

Miikka Niittyvuopio[1], Suvi Vaara[2], Pasi Ohtonen[1], Ville Pettilä[2], Janne Liisanantti[1], Tero Ala-Kokko[1]

1 Division of Intensive Care Medicine, Study Group of Surgery, Anesthesiology and Intensive Care Medicine, Oulu University Hospital and Medical Research Center Oulu, Oulu, Finland
2 Division of Intensive Care Medicine, Department of Anesthesiology, Intensive Care and Pain Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Corresponding author:
Dr Miikka Niittyvuopio
Oulu University Hospital
Department of Anesthesiology and Intensive Care
PO BOX 21
90029 Oulu, Finland
e-mail: miikka.niittyvuopio@ppshp.fi

Author contribution statement:

Miikka Niittyvuopio: Writing - original draft - review and editing, visualization and formal analysis.

Suvi Vaara: Data curation, conceptualization and supervision.

Pasi Ohtonen: Methodology, formal analysis and writing - review and editing.

Ville Pettilä: Conceptualization, supervision and project administration.

Janne Liisanantti: Conceptualization.

Tero Ala-Kokko: Writing - review and editing, conceptualization, supervision, project administration and validation.

Abstract

Background

Data on the causes of death and long-term mortality of intensive care unit-treated hospital survivors with acute kidney injury (AKI) are limited. The goal of this study was to analyze the

causes of death among critically ill patients during a 5-year follow-up.

Methods

In this predetermined sub-study of a prospective, observational, multi-center cohort from the FINNAKI study, we analyzed 2436 patients who were discharged from the hospital. Statistics Finland provided the follow-up data and causes of death.

Results

During the follow-up, 765 (31%) patients died, of whom 295 (39%) had AKI and 73 (9.5%) had received renal replacement therapy. More than half of the deaths in both the non-AKI and AKI groups occurred after the one year follow-up (58 vs. 54 %, respectively). The three most common causes of death in AKI were cardiovascular diseases (36%), malignancies (21%), and neurological diseases (11%). In early deaths (< 90 days) cardiovascular causes were more prevalent in AKI patients compared to non-AKI (38 % vs. 25 %, p=0.037.) In six cases (0.8 %), the main cause of death was kidney disease, out of which 5 were in the AKI group. In patients with cardiovascular causes, the median time to death was shorter in AKI patients compared to non-AKI patients (508 vs 816 days, p=0.018).

Conclusion

Cardiovascular causes and malignancies account for more than half of the causes of death in patients who had suffered AKI, while death from kidney disease after AKI is rare. Early cardiovascular deaths are more prevalent in AKI compared to non-AKI patients.

Keywords: acute kidney injury, renal replacement therapy, causes of death

Editorial Comment

In this large study in survivors after intensive care in Finland, the researchers found one year mortality of 31%, and 39% of all deaths were in the AKI group. The most frequent cause of death was cardiovascular disease, and only 6 died from kidney disease.

Introduction

The incidence of acute kidney injury (AKI) has been increasing worldwide during the last few decades.[1] The current incidence of AKI among critically ill adult patients is 34–57%.[2,3] The condition is associated with increased short- and long-term mortality rates, morbidity, and long-term adverse outcomes such as chronic kidney disease, end-stage renal disease (ESRD), and heart failure.[3–5] The reported long-term mortality after AKI varies between 21% and 64%.[6–10]

Data on the causes of death during the long-term follow-up period in intensive care unit (ICU)-treated hospital survivors are limited. Previous studies on ICU-treated hospital survivors have been single-center studies with a 1-year follow-up[11] or retrospective.[12] The most recent studies on AKI patients have been conducted in patients hospitalized with AKI[13] or have included hospitalized patients who died during the hospital stay.[6] Sepsis, cardiovascular causes and cancer have been the most common causes of deaths in these previous studies.[6,13]

The goal of this prospective nationwide multicenter study was to evaluate the causes of death among critically ill patients with or without AKI admitted to 17 ICUs, during a 5-year follow-up after hospital discharge.

Methods

This study was a predetermined sub-study of the Finnish Acute Kidney Injury (FINNAKI) study, which was conducted as a prospective multi-center cohort study in 17 Finnish ICUs between September 1, 2011 and February 1, 2012.[14] The FINNAKI study protocol was approved by the Ethics Committee of the Department of Surgery at Helsinki University Hospital (Helsinki, Finland), and written consent for the study was provided by the participating patients or their proxies. The Finnish National Institute of Health and Welfare approved data collection considering deceased patients if an informed consent could not be obtained.

Clinical data were collected prospectively during the study period by using a study-specific case report form and the Finnish Intensive Care Consortium's database (Tieto Ltd.) The collected data included information considering the peri-ICU clinical data (patient demographics, physiological parameters, ICU severity scores, International Classification of Diseases, 10th Edition (ICD-10) diagnoses, length of stay, and in-hospital mortality) of every patient admitted to the participating ICUs. In the current study, survival data were followed from the hospital discharge up to 5 years. Mortality data were provided by the Finnish Population Register Centre which provides an electronic national register containing basic information about Finnish citizens and foreign citizens residing permanently in Finland. The causes of death were provided by the Finnish Cause of Death registry (FCDR) according to the ICD-10. In Finland, a forensic pathologist verifies the correctness of all death certificates issued.

Patients

All adult patients (>18 years of age) with an emergency ICU admission of any duration, as well as adult patients with an elective ICU admission expected to last more than 24 hours, were included. The excluded patient groups were: (1) those with ESRD with maintenance RRT; (2) re-admitted patients who had received RRT during their previous ICU admission; (3) patients who were treated as potential organ donors, (4) patients receiving intermediate care; (5) elective post-surgical patients with an expected length of stay less than 24 hours; (6) patients not permanently living in Finland; (7) patients unable to provide consent in Finnish or Swedish; (8) patients who were transferred from one hospital to another if they were already recruited to the study in a referring hospital; and (9) patients younger than 18 years of age. Each patient was included one time only.

This analysis was performed on the patients who were discharged from hospital. No other exclusions criteria were used.

Definitions

AKI was defined and classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria[15] considering plasma creatinine and urine output criteria. RRT was defined as either continuous or intermittent. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine criteria.[16] The ICU scoring systems used to measure the severity of illness included the Acute Physiology And Chronic Health Evaluation II (APACHE II),[17] Simplified Acute Physiology Score[18] and Sequential Organ Failure Assessment Score[19] scoring systems. Time to death was categorized as less than 90 days (early), 3 months to 365 days and more than 365 days (late). Long term outcome was defined as outcome over a five-year period.

Statistical analysis

We performed the statistical analyses using the SPSS software program for Windows (version 21.0; IBM Corp., Armonk, NY, USA). We expressed the statistics for continuous variables as medians with 25th and 75th percentiles and categorical variables as absolute numbers and percentages (%). We tested the continuous variables using the Kruskal-Wallis H-test and

categorical variables using the Pearson's chi-square test. We created Kaplan-Meier survival curves. A multivariable adjusted Cox model was calculated to assess the impact of AKI on five year survival. This included age, number of chronic diseases, type of admission and status of severe sepsis as adjusting variables. The results of the Cox model are presented as hazard ratios with 95% confidence interval (95% CI). The follow-up started from the day of discharge and ended at 5 years or on the day of death. P-values less than 0.05 were considered statistically significant.

Results

A total of 2436 of 2901 (84.0%) FINNAKI patients were discharged from the hospital and included in the analysis. A flowchart depicting the patient enrollment process is presented in Figure 1. The incidence of AKI in the entire study population was 34.4 % (n=838). The proportions of KDIGO stages 1-3 were: Stage 1 16.3% (n=398), stage 2 6.9% (n=169), and stage 3 11.1% (n=271). During the 5-day ICU data collection period, 8.0% (n=196) patients received RRT. The patients with AKI were older, had more chronic comorbidities, were more likely to receive mechanical ventilation and vasoactive medication, and were more often admitted due to sepsis (Table 1).

During the 5-year follow-up period, 765 of the 2436 (31.4%) patients died. Of the deceased patients, 295/765 (38.6%) had AKI during their ICU stay and 73/765 (9.5%) received RRT because of AKI during the ICU period. The 5-year mortality rate of the patients with AKI was

35.0 % (295/838) in contrast to 29.4% (470/1598) in patients without AKI (p=0.003). The corresponding 5-year mortality rates for those AKI patients who received and did not receive RRT for AKI were 37.2% (73/196) and 34.6% (222/642; p=0.494), respectively. The five-year mortality rates according to KDIGO groups were: KDIGO 1 32.9 %; KDIGO 2 36.1 % and KDIGO 3 38.0 % (p=0.385).

The main causes of death in the entire cohort were cardiovascular (33.2%, n=254), malignancies (21.7%, n=166) and neurological (13.2%, n=101). There were no differences in the causes of death between AKI and non-AKI patients. (Table 2). There was also no difference in cardiovascular diseases as a main cause of death in patients with RRT compared to the non-AKI and AKI groups without RRT (42.5% vs. 31.70% vs. 33.3% p=0.192). However, cardiovascular causes were more prevalent in early deaths in AKI patients compared to non-AKI (36/94; 38 % vs. 30/120; 25 %, p=0.037) (Table 3). Only 6 of the deceased patients had their main cause of death classified as kidney disease and out of these 5 had AKI during their ICU treatment. Only one of the six renal causes occurred in less than one year of follow-up. There were 5 late deaths due to infection out of which 4 occurred in AKI patients.

Among the deceased patients who were admitted to the ICU due to cardiovascular causes the proportion of cardiovascular disease as a cause of death was 57.7 %. The proportion of neurological causes of death was 39.0 % within the deceased patients originally admitted to the ICU due to neurological causes. The deceased patients originally admitted to the ICU due to trauma died of traumatic causes in 45.8 % of cases. In the poisoning admission group, 38.5 % patients had poisoning as a primary cause of death. In those with malignancy as a co-morbidity the proportion of cancer as a primary cause of death was 56.3 %.

More than half of deaths occurred after one year of follow-up in both groups (271/470; 58 % in no AKI and 158/295; 54 % in AKI). The median time to death was 507 days (IQR 74–1122): 526 (86–1130) days in the non-AKI group, 435 (47–1050) days in the AKI group, and 450 (52–1303) days in the RRT group (p=0.231) (Figure 2). In patients dying of cardiovascular causes, the median time to death was shorter in AKI patients as compared to non-AKI patients (508 vs 816 days, p=0.018) (Table 4).

According to the multivariable adjusted Cox model hazard ratio for AKI not requiring RRT, death was 1.03 (95% CI 0.87 to 1.21, p=0.75) and for AKI with RRT death was 1.17 (95% CI 0.91 to 1.51, p=0.22) compared to patients without AKI (Table 5).

Discussion

During the 5-year follow-up around one third of patients died in both the non-AKI and the AKI groups. Cardiovascular causes and malignancies were common, but kidney disease was rare as a cause of death after AKI. Cardiovascular causes were more prevalent among early deaths in AKI patients compared to non-AKI patients.

Our study was prospective and had a long and complete 5-year follow-up of hospital survivors after critical illness. In our series, the 5-year mortality of those with AKI was 35 % and those that required RRT was 37 %. Compared to our study, which included all AKI patients, the 5-year mortality was higher in a prospective single-center study conducted among ICU survivors with KDIGO stage one AKI (56%).[8] In contrast to our series, in their study the proportion of stage 3 AKI was higher (26 % vs. 11 %). In a single-center study from the 1990s, the 5-year mortality rate in hospital survivors with AKI requiring RRT was given as 53%.[20] The corresponding mortality in our series was 37 %.

In our series, one-third of the deaths in non-AKI and AKI groups were caused by cardiovascular causes. In general adult intensive care population malignancies have been reported to account for a third (33 %) of the causes of death while cardiovascular causes are the second most common cause of death (24 %).[21] We had a low prevalence of malignancies as a comorbid condition in our series (7 %). Furthermore, in our series the cause of death was related to the initial admission diagnosis in cardiovascular, neurological, trauma and poisoning cases, while cancer as a cause of death was related to malignant comorbidity.

In our series there was no difference in cardiovascular mortality between non-AKI and AKI patients. However, cardiovascular causes were more prevalent among early deaths in AKI patients compared to non-AKI patients. Furthermore, patients with RRT had an 11 % higher prevalence of CV mortality compared to non-AKI patients. This is not surprising since in our population non-AKI patients had less comorbidities, were younger, more commonly female and were less severely

ill on admission compared to AKI. However, it has been shown that AKI is associated with an 86% increased risk of cardiovascular mortality and a 38% increased risk of major cardiovascular events.[22] In a recently published population-based Canadian study with a 1-year follow-up of patients hospitalized with AKI, the most common causes of death were cardiovascular diseases (28%) and cancer (28%) .[13] Our results are similar to those reported in the Canadian study, although in our AKI population sepsis on admission was more frequent (41 % vs. 4 %) and RRT was more frequently applied (30 % vs. 5 %) compared to the Canadian study. However, in the Canadian material, cardiovascular comorbidities and diabetes were higher compared to our series (79 % vs. 26 % and 46 % vs. 26 %). In the same study, cancer deaths were more prevalent as an early case compared to our material (28 % vs. 16 %). This is explained by the fact that cancer as comorbidity in AKI patients was more prevalent in their material as compared to our material (18 % vs. 7.2 %).

In our study the main factors in the multivariate analysis associated with five year mortality were older age, number of chronic comorbidities and emergency type of an admission. AKI and RRT alone were not associated with mortality. Also, in a large systematic review of the literature and a meta-analysis conducted in a study design among all hospitalized patients with AKI, it was reported that increased age, and chronic medical comorbidities were significantly associated with a increased mortality rate in multivariate analysis.[23]

This study has the following strengths. First, 5-year mortality data and causes of deaths were retrieved from the FCDR with a complete follow-up. Thus, we consider our results reliable. Second, our study was a large, prospective, nationwide multi-center study comprising ICU-admitted AKI patients who survived to hospital discharge. Therefore, our results are representative and generalizable. The main limitation is that the recording of the causes of death is register-based and done for administrative and legal purposes instead of prospectively defined for the study. The causes of deaths from the FCDR are based on Finnish death certificates filled out by the treating physician or a forensic medicine specialist. However, the Finnish death certificate has been reported to be reliable and of high quality.[24,25] Secondly, we do not have temporal long-term information on each patient's morbidity which obviously has an impact on the causes of death. Finally, we do not have an age- and sex-matched control population since others have shown that cancer-related deaths occur at higher rates in AKI than in the general population.[13] However,

according to the statistics Finland, the prevalence of cancer in the overall Finnish population above 15 years of age in 2016 as a main cause of death is similar to that in our AKI population (23 % vs. 21 %).[26]

Conclusions

Cardiovascular causes and neoplasms account for more than half of the causes of death in AKI while death from kidney disease after AKI is rare. Early cardiovascular deaths are more prevalent in AKI compared to critically ill non-AKI patients.

Funding

No financial support was provided for this sub-study.

Conflict of interest

The authors have no conflicts of interest

REFERENCES

1. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, Liu KD, Mehta RL, Pannu N, Van Biesen W, Vanholder R. Acute kidney injury: an increasing global concern. Lancet 2013; 382:170-9.

2. Chang CH, Fan PC, Chang MY, Tian YC, Hung CC, Fang JT, Yang CW, Chen YC. Acute kidney injury enhances outcome prediction ability of sequential organ failure assessment score in critically ill patients. PLoS One 2014; 9:e109649.

3. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honore PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41:1411-23.

4. Newsome BB, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, Allison JJ. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med 2008; 168:609-16.

5. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, Ray JG, University of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009; 302:1179-85.

6. Selby NM, Kolhe NV, McIntyre CW, Monaghan J, Lawson N, Elliott D, Packington R, Fluck RJ. Defining the cause of death in hospitalised patients with acute kidney injury. PLoS One 2012; 7:e48580.

7. Gallagher M, Cass A, Bellomo R, Finfer S, Gattas D, Lee J, Lo S, McGuinness S, Myburgh J, Parke R, Rajbhandari D, POST-RENAL Study Investigators and the ANZICS Clinical Trials

Group. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS Med 2014; 11:e1001601.

8. Linder A, Fjell C, Levin A, Walley KR, Russell JA, Boyd JH. Small acute increases in serum creatinine are associated with decreased long-term survival in the critically ill. Am J Respir Crit Care Med 2014; 189:1075-81.

9. Mildh H, Pettila V, Korhonen AM, Karlsson S, Ala-Kokko T, Reinikainen M, Vaara ST, FINNAKI Study Group. Three-year mortality in 30-day survivors of critical care with acute kidney injury: data from the prospective observational FINNAKI study. Ann Intensive Care 2016; 6:118,016-0218-5. Epub 2016 Nov 29.

10. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol 2010; 21:345-52.

11. Mayr VD, Dunser MW, Greil V, Jochberger S, Luckner G, Ulmer H, Friesenecker BE, Takala J, Hasibeder WR. Causes of death and determinants of outcome in critically ill patients. Crit Care 2006; 10:R154.

12. Hicks PR, Mackle DM. Cause of death in intensive care patients within 2 years of discharge from hospital. Crit Care Resusc 2010; 12:78-82.

13. Silver SA, Harel Z, McArthur E, Nash DM, Acedillo R, Kitchlu A, Garg AX, Chertow GM, Bell CM, Wald R. Causes of Death after a Hospitalization with AKI. J Am Soc Nephrol 2018; 29:1001-10.

14. Nisula S, Kaukonen KM, Vaara ST, Korhonen AM, Poukkanen M, Karlsson S, Haapio M, Inkinen O, Parviainen I, Suojaranta-Ylinen R, Laurila JJ, Tenhunen J, Reinikainen M, Ala-Kokko T, Ruokonen E, Kuitunen A, Pettila V, FINNAKI Study Group. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med 2013; 39:420-8.

15. Section 2: AKI Definition. Kidney Int Suppl (2011) 2012; 2:19-36.

16. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G, International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 2003; 29:530-8.

17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13:818-29.

18. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957-63.

19. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996; 22:707-10.

20. Schiffl H, Lang SM, Fischer R. Long-term outcomes of survivors of ICU acute kidney injury requiring renal replacement therapy: a 10-year prospective cohort study. Clin Kidney J 2012; 5:297-302.

21. Mayr VD, Dünser MW, Greil V, Jochberger S, Luckner G, Ulmer H, Friesenecker BE, Takala J, Hasibeder WR. Causes of death and determinants of outcome in critically ill patients. Crit Care. 2006; 10(6): R154.

22. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, Hunn BH. AKI and Long-Term Risk for Cardiovascular Events and Mortality. J Am Soc Nephrol 2017; 28:377-87.

23. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;53(6):961-973.

24. Lahti RA, Penttila A. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. Forensic Sci Int 2001; 115:15-32.

25. Lahti RA, Penttila A. Cause-of-death query in validation of death certification by expert panel; effects on mortality statistics in Finland, 1995. Forensic Sci Int 2003; 131:113-24.

26. Official Statistics of Finland. Official statistics of finland (OSF): Causes of death [e-publication]. ISSN=1799-5078. 2016, appendix table 2a. deaths by underlying cause of death and by age in 2016, both sexes.helsinki: Statistics Finland 2017. 2017.

Table 1. Patient demographics and clinical data categorized to patient groups with or without AKI and AKI patients with or without RRT.

	Data available	All (n=2436)	No AKI (n=1598)	AKI (n=838)	p-value	AKI without RRT (n=642)	AKI and RRT (n=196)	p-value
Age, median (IQR)	2436	62 (50-72)	61 (48.0-72.0)	64 (53.8-74.0)	p<0.001	64 (54.0-74.0)	63 (52.0-71.0)	p=0.028
Age 18-65, n (%)	2436	1435 (58.9%)	973 (60.9%)	462 (55.1%)	p=0.020	340 (53.0%)	122 (62.2%)	p=0.055
Age 66-79, n (%)	2436	757 (31.1%)	476 (29.8%)	281 (33.5%)		223 (34.7%)	58 (29.6%)	
Age 80-, n (%)	2436	244 (10.0%)	149 (9.3%)	95 (11.3%)		79 (12.3%)	16 (8.2%)	
Male, n (%)	2436	1546 (63.5%)	990 (62.0%	556 (66.3%)	p=0.032	423 (65.9%)	133 (67.9%)	p=0.610
Dead at five years after hospital discharge, n(%)	2436	765 (31.4%)	470 (29.4%)	295 (35.2%)	p=0.003	222 (34.6 %)	73 (37.2%)	p=0.494
Emergency admission, n (%)	2405	2088 (86.8%)	1370 (86.8%)	718 (86.9%)	p=0.912	542 (85.5%)	176 (91.7%)	p=0.026
SOFA-score (admission), median (IQR)	2436	7 (4-9)	6 (4-8)	8 (6-10)	p<0.001	7 (6-10)	10 (7-12)	p<0.001
SOFA-score (maximum), median (IQR)	2436	7 (5-9)	6 (4-8)	8 (6-11)	p<0.001	8 (6-10)	10 (8-12)	p<0.001
SAPS II-score (24 h), median	2436	34 (26-45)	32 (25-42)	39 (31-50)	p<0.001	37 (30-47)	46 (36-56)	p<0.001

Table 1. Patient demographics and clinical data categorized to patient groups with or without AKI and AKI patients with or without RRT.

(IQR)								
Severe sepsis, n (%)	2436	671 (27.5%)	331 (20.7%)	340 (40.6%)	p<0.001	261 (40.7%)	79 (40.3%)	p=0.931
Received norepinephrine, n (%)	2436	1375 (56.4%)	793 (49.6 %)	582 (69.5%)	p<0.001	437 (68.1%)	145 (74.0%)	p=0.116
Received mechanical ventilation, n(%)	2436	1617 (66.4 %)	1023 (64 %)	594 (70.9%)	p=0.001	465 (72.4%)	129 (65.8 %)	p=0.074
ICU LOS, days, median (IQR)	2435	2.5 (1.2-5.0)	1.9 (1.0-3.9)	3.9 (2.1-6.9)	p<0.001	3.6 (2.0-5.5)	6.0 (2.7-11.6)	p<0.001
Baseline creatinine, median, umol per litre (IQR)	1532	75 (61-91)	73 (59-89)	78 (64-97)	p<0.001	76 (62-91)	91 (71-116)	p<0.001
No comorbidities, n (%)	2436	884 (36.3%)	632 (39.5%)	252 (30.1%)	p<0.001	192 (29.9%)	60 (30.6%)	p=0.528
One comorbidity, n (%)	2436	639 (26.2%)	441 (27.6%)	198 (23.6%)		159 (24.8%)	39 (19.9%)	
Two comorbidities, n (%)	2436	507 (20.8%)	309 (19.3%)	198 (23.6%)		147 (22.9%)	51 (26.0%)	
Three or more comorbidities, n (%)	2436	406 (16.7%)	216 (13.5%)	190 (22.7%)		144 (22.4%)	46 (23.5%)	
COPD, n (%)	2421	214 (8.8%)	135 (8.5%)	79 (9.5%)	p=0.403	66 (10.4%)	13 (6.7%)	p=0.122
Hypertension, n (%)	2420	1121 (46.3%)	665 (41.9%)	456 (54.8%)	p<0.001	351 (55.1%)	105 (53.8%)	p=0.758
MCC or ASO, n (%)	2412	292 (12.1%)	167 (10.6%)	125 (15.1%)	p=0.001	95 (15.0%)	30 (15.4%)	p=0.885

Table 1. Patient demographics and clinical data categorized to patient groups with or without AKI and AKI patients with or without RRT.

Heart failure, n (%)	2415	244 (10.1%)	147 (9.3%)	97 (11.7%)	p=0.056	73 (11.5%)	24 (12.4%)	p=0.728
Diabetes mellitus, n (%)	2436	535 (22.0%)	315 (19.7%)	220 (26.3%)	p<0.001	153 (23.8%)	67 (34.2%)	p=0.004
Non-metastatic malignancy, n (%)	2415	175 (7.2%)	113 (7.1%)	62 (7.5%)	p=0.759	51 (8.0%)	11 (5.7%)	p=0.518
Chronic kidney disease, n (%)	2426	144 (5.9%)	61 (3.8%)	83 (10.0%)	p<0.001	53 (8.3%)	30 (15.5%)	p=0.004
Rhabdomyolysis, n (%)	2427	58 (2.4%)	28 (1.8%)	30 (3.6%)	p=0.005	17 (2.7%)	13 (6.7%)	p=0.009
Acute liver failure, n (%)	2434	41 (1.7%)	18 (1.1%)	23 (2.8%)	p=0.003	12 (1.9%)	11 (5.6%)	p=0.005
Cardiogenic shock, n (%)	2432	80 (3.3%)	43 (2.7%)	37 (4.4%)	p=0.023	26 (4.1%)	11 (5.6%)	p=0.356
Pre ICU RRT, n (%)	2422	8 (0.3%)	2 (0.1%)	6 (0.7%)	p=0.015	0 (0.0%)	6 (3.1%)	p<0.001
Pre ICU radiocontrast, n (%)	2421	590 (24.4%)	413 (26.0%)	177 (21.3%)	p=0.011	143 (22.4%)	34 (17.5%)	p=0.143

AKI: Acute kidney injury; RRT: Renal replacement therapy; SOFA: Sequential Organ Failure Assessment; SAPS II: Simplified Acute Physiology Score II; LOS: Length of stay; COPD: Chronic obstructive pulmonary disease; MCC: Coronary artery disease; ASO: Atherosclerosis.
Categorical variables are analyzed using Pearson´s Chi-square test. Continuous variables are expressed as medians with 25th and 75th percentile and the analysis between groups was done by the Mann-Whitney U test.

Table 2. Causes of deaths categorized to patient groups with or without AKI and AKI patients with or without RRT.

Diagnose group	All (n=765)	No AKI (n=470)	AKI (n=295)	p-value	AKI without RRT (n=222)	AKI and RRT (n=73)	p-value
Cardiovascular diseases, n(%)	254 (33.2%)	149 (31.70%)	105 (35.6%)	p=0.266	74 (33.3%)	31 (42.5%)	p=0.192
Cancer, n(%)	166 (21.7%)	105 (22.3%)	61 (20.7%)	p=0.587	46 (20.7%)	15 (20.5%)	p=0.863
Neurologic diseases, n(%)	101 (13.2%)	68 (14.5%)	33 (11.2%)	p=0.192	29 (13.1%)	4 (5.5%)	p=0.108
Gastrointestinal diseases, n(%)	63 (8.2%)	35 (7.4%)	28 (9.5%)	p=0.317	20 (9.0%)	8 (11.0%)	p=0.528
Trauma, n(%)	47 (6.1%)	33 (7.0%)	14 (4.7%)	p=0.202	13 (5.9%)	1 (1.4%)	p=0.170
Pulmonary diseases, n(%)	41 (5.4%)	30 (6.4%)	11 (3.7%)	p=0.113	10 (4.5%)	1 (1.4%)	p=0.167
Infection, n(%)	27 (3.5%)	14 (3.0%)	13 (4.4%)	p=0.297	10 (4.5%)	3 (4.1%)	p=0.574
Other, n(%)	21 (2.7%)	11 (2.3%)	10 (3.4%)	p=0.387	8 (3.6%)	2 (2.7%)	p=0.637
Poisonings, n(%)	18 (2.4%)	13 (2.8%)	5 (1.7%)	p=0.341	3 (1.4%)	2 (2.7%)	p=0.505
Metabolic, n(%)	13 (1.7%)	6 (1.3%)	7 (2.4%)	p=0.253	3 (1.4%)	4 (5.5%)	p=0.032
Psychiatric, (%)	8 (1.0%)	5 (1.1%)	3 (1.0%)	p=0.951	3 (1.4%)	0 (0.0 %)	p=0.615
Renal, n(%)	6 (0.8 %)	1 (0.2%)	5 (1.7 %)	p=0.024	3 (1.4 %)	2 (2.7 %)	p=0.039

Table 2. Causes of deaths categorized to patient groups with or without AKI and AKI patients with or without RRT.

Categorical variables are analyzed using Pearson´s Chi-square test.

Table 3. Causes of deaths categorized into three groups according to the time to death

	< 90 days (n=214)			90-365 days (n=122)			≥365 days (n=429)		
	AKI	**Non-AKI**	**p-value**	**AKI**	**Non-AKI**	**p-value**	**AKI**	**Non-AKI**	**p-value**
Cardiovascular disease.	36 (54.5%)	30 (45.5%)	p=0.037	12 (36.4%)	21 (63.6%)	p=0.875	57 (36.8%)	98 (63.2%)	p=0.986
Cancer	11 (31.4%)	24 (68.6%)	p=0.103	13 (31.7%)	28 (68.3%)	p=0.561	37 (41.1%)	53 (58.9%)	p=0.344
Neurologic disease	8 (29.6%)	19 (70.4%)	p=0.109	4 (28.6%)	10 (71.4%)	p=0.578	21 (35.0%)	39 (65.0%)	p=0.751
Gastro-intestinal disease	16 (59.3%)	11 (40.7%)	p=0.086	4 (50.90%)	4 (50.0%)	p=0.366	8 (28.6%)	20 (71.4%)	p=0.349
Trauma	5 (26.3%)	14 (73.7%)	p=0.105	2 (28.6%)	5 (71.4%)	p=0.703	7 (33.3%)	14 (66.7%	p=0.733
Pulmonary disease	3 (33.3%)	6 (66.7%)	p=0.513	1 (20.0%)	4 (80.0%)	p=0.466	7 (25.9%)	20 (74.1%)	p=0.225
Infection	7 (41.2%)	10 (58.8%)	p=0.812	2 (40.0%)	3 (60.0%)	p=0.820	4 (80.0%)	1 (20.0%)	p=0.044
Other	4 (80.0%)	1 (20.0%)	p=0.100	3 (75.0%)	1 (25.0%)	p=0.091	3 (25.0%)	9 (75.0%)	p=0.389
Poisoning	1 (25.0%)	3 (75.0%)	p=0.441	0 (0.0%)	0 (0.0%)	n/a	4 (28.6%)	10 (71.4%)	p=0.515
Metabolic	2 (66.7%)	1 (33.3%)	p=0.424	1 (33.3%)	2 (66.7%)	p=0.944	4 (57.1%)	3 (42.9%)	p=0.261
Psychiatric disease	1 (50.0%)	1 (50.0%)	p=0.862	0 (0.0%)	1 (100.0%)	p=0.459	2 (40.0%)	3 (60.0%)	p=0.882

Table 3. Causes of deaths categorized into three groups according to the time to death

Renal	0 (0.0%)	0 (0.0%)	n/a	1 (100.0%)	0 (0.0%)	p=0.174	1 (20.0%)	4 (80.0%)	p=0.044

Categorical variables are analyzed using Pearson´s Chi-square test.

Table 4. Time to death according to the causes of death in Non-AKI and AKI groups.

Cause of death main group:	Total	Non-AKI	AKI	p-value
Cardiovascular disease.	645 (82-1202)	816 (169-1256)	508 (38-1067)	p=0.018
Cancer	408 (110-931)	368 (109-839)	512 (109-1148)	p=0.246
Neurologic disease	620 (78-1230)	528 (61-1196)	926 (96-1320)	p=0.300
Gastrointestinal disease	110 (37-853)	564 (47-1121)	52 (26-514)	p=0.070
Trauma	179 (29-708)	115 (25-952)	696 (387-1297)	p=0.981
Pulmonary disease	712 (182-1274)	760 (175-1285)	610 (49-878)	p=0.659
Infection	712 (182-1274)	72 (42-166)	85 (44-912)	p=0.528
Other	595 (100-1255)	1255 (595-1586)	107 (44-525)	p=0.006
Poisoning	898 (408-1533)	555 (247-1571)	1308 (545-1516)	p=0.730
Metabolic	652 (101-887)	482 (217-1011)	795 (75-1190)	p=0.886
Psychiatric disease	613 (167-1039)	423 (156-926)	1028 (535-1369)	p=0.456
Renal	842 (706-1216)	706 (706-706)	847 (469-1285)	p=0.380

Continuous variables are expressed as medians with 25th and 75th percentile and the analysis between groups was done using the

Table 4. Time to death according to the causes of death in Non-AKI and AKI groups.

Mann-Whitney U test.

Table 5. Multivariate hazard ratios and 95% CI for mortality during the five-year follow-up.

No Aki	1.0	
AKI	1.03 (0.87 to 1.21)	p=0.75
AKI requiring RRT	1.17 (0.91 to 1.51)	p=0.22
AGE 18-65 years	1	
Age 66-79 years	1.99 (1.68-2.35)	p<0.001
Age over 80 years	3.1 (2.51-3.84)	p<0.001
No comorbidities	1	
One comorbidity	1.44 (1.17-1.77)	p<0.001
Two comorbidities	1.63 (1.31-2.02)	p<0.001
Three or more comorbidities	2.41 (1.92-3.01)	p<0.001
Emergency admission	1.73 (1.38-2.18)	p<0.001

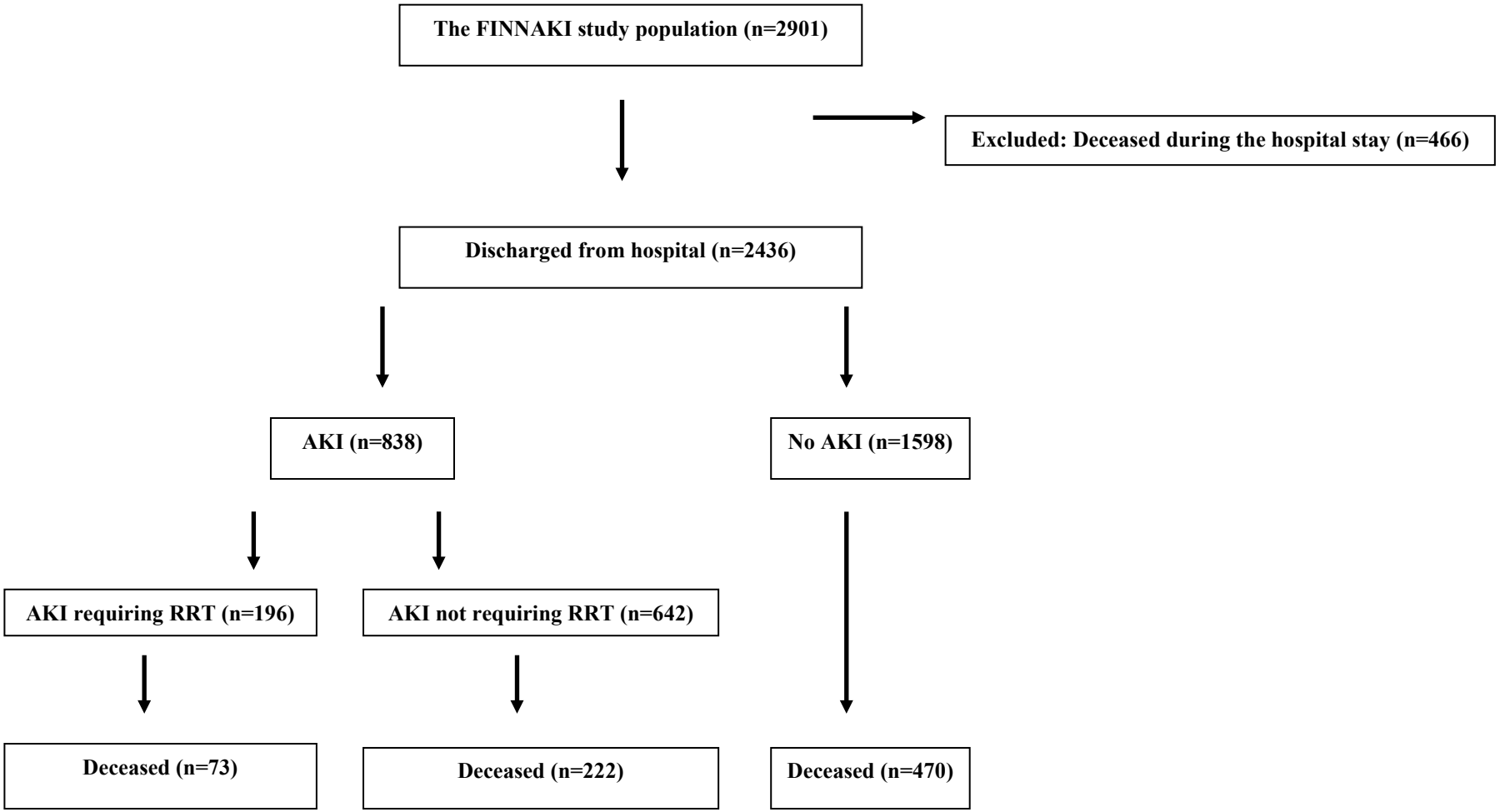
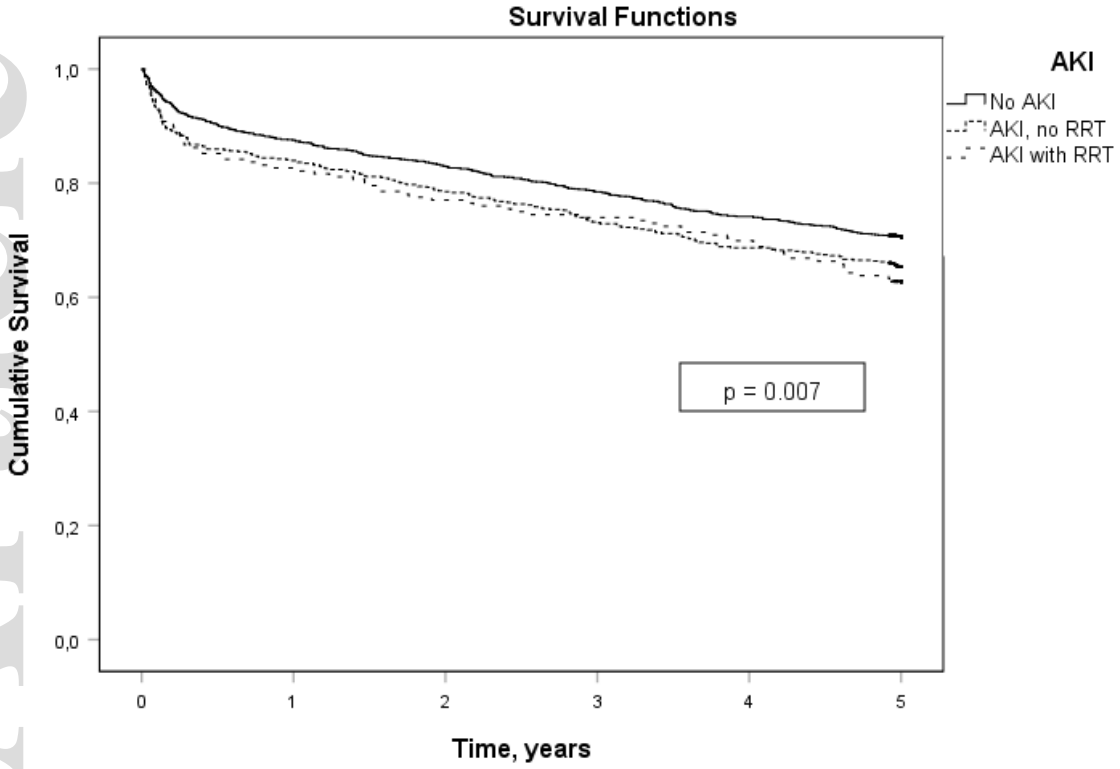


Figure 1. Outline of the study´s patient recruitment

Figure 2 The Kaplan-Meier plots presenting the unadjusted survival rates of the patients without AKI, with AKI not requiring RRT and with AKI requiring RRT. P-value according to log-rank test



Diagnostic group	All n=765	No AKI n=470	AKI no RRT n=222	AKI and RRT n=73	p-value
Time to death, days, median (IQR)	507 (74-1122)	525 (86-1130)	435 (47-1050)	450 (52-1303)	p=0.231

Continuous variables are expressed as medians with 25th and 75th percentile and the analysis between groups was done by the Mann-Whitney U test.