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RAPID OCCURRENCE OF CHRONIC KIDNEY DISEASE IN PATIENTS EXPERIENCING REVERSIBLE ACUTE KIDNEY INJURY AFTER CARDIAC SURGERY

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Running title*: AKI and CKD following cardiopulmonary bvypass*

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ABSTRACT

Background There is recent evidence to show that patients suffering from acute kidney injury (AKI) are at increased risk of developing chronic kidney disease (CKD), despite the fact that surviving tubular epithelial cells have the capacity to fully regenerate renal tubules and restore renal function within days or weeks. The aim of the study was to investigate the impact of AKI on *de novo* CKD.

Methods We conducted a retrospective population-based cohort study of patients initially free from CKD, who were scheduled for elective cardiac surgery with cardiopulmonary bypass, and who developed an episode of AKI from which they recovered. The study was conducted at two French university hospitals between 2005 and 2015. These individuals were matched with patients without AKI according to a propensity score for developing AKI.

Results Among the 4791 patients meeting our inclusion criteria, 1375 (29%) developed AKI, and 685 fully recovered. Propensity score matching was used to balance the distribution of covariates between AKI and non-AKI control patients. Matching was possible for 597 cases. During follow-up, 34(5.7%) had reached a diagnosis of CKD, as opposed to 17 (2.8%) in the control population (HR=2.3; bootstrapping 95%CI= [1.9–2.6]).

Conclusions Our data consolidate the recent paradigm shift, reporting AKI as a strong risk factor for the rapid development of CKD.

Keywords (3-5): acute kidney injury; chronic kidney disease; ischemia reperfusion

INTRODUCTION

Ten years ago, international experts from the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN) proposed a unique definition of "Acute Kidney Injury" (AKI). Thus, a diagnosis of AKI requires either a 1.5-fold increase in serum creatinine within 7 days, or serum creatinine increase by more than 0.3 mg/dL (26.5 µmol/L) within 48 hours.[1] Following this consensus, two unexpected findings have been reported. First, even a mild episode of AKI was found to increase the risk of death, independent of any comorbidities.[2-5] Second, as evidenced by four independent studies, AKI was found to be a major risk factor for the development of a chronic kidney disease (CKD) within a matter of a few weeks.[6-9] Whereas the progressive decrease in the residual renal function of patients who did not fully recover from an episode of severe AKI is intuitive, this observation is less immediately obvious in the case of patients who recovered "*ad integrum*". Nonetheless, retrospectively exploring the long-term renal prognosis of a recovering AKI, in unselected patients who were CKD-free at the time of the acute episode, Jones[10] and Bucaloiu[11] have found a 2- to 3-fold increase in the risk of developing post-AKI stage 3 CKD.

In addition, experimental data have recently highlighted molecular mechanisms at stake in myofibroblasts as well as in tubular epithelial cells, linking AKI with CKD.[12-14]

Regarding the studies mentioned above, some methodological issues need to be emphasized. First, patients could have been included on the basis of various pathological conditions, including the chronic conditions of multiple kidney injury.[6-11] Second, the recovery of AKI was not systematically verified.[6-9] Hence, CKD could have been present simply as a result of a sequel, and of immediate scarring. Finally, the diagnosis of CKD could have been defined by a diagnostic code and not by numerical values estimating the glomerular filtration rate (GFR).[6-9]

A study aiming at the consolidation of the recent knowledge that a recovering AKI may lead to CKD would ideally test a population of patients: a) at risk of AKI, b) exposed to a unique event leading to AKI, and c) in whom renal function would be estimated both before and after an episode of AKI. Incidence of AKI after cardiac surgery varies between 15 and 45%.[15-19] Although a pre-existing CKD is an established risk factor for AKI in this context, AKI may occur in CKD-free patients.[2, 17] We analyzed the renal outcome of CKD-free patients scheduled for cardiopulmonary bypass (CBP) cardiac surgery at two centers in France, who did or did not develop AKI with a recovering renal function identical (±10%) to that before surgery.

MATERIAL AND METHODS

Study Design

We conducted a bicenter retrospective cohort study with a propensity score matching analysis. The study took place at two French university hospitals, within a catchment area of about 13.5 million people. Each year, both centers conduct 5% of the total cardiac surgery in France. The universal public health insurance guarantees equal access and free primary health care to all French citizens. The study was carried out in accordance with the principles outlined in the Declaration of Helsinki after approval from the institutional review board (approval number: SFAR 00010254-2016-072) at each participating center.

Estimated GFR

Serum creatinine concentrations were measured using the Jaffé method. GFR values were estimated (eGFR) using the Modification of Diet in Renal Disease (MDRD) creatinine equation.[20] When the test was ID/MS standardized, a correction was applied to the MDRD equation.[21]Baseline eGFR was defined by the MDRD calculated with the serum creatinine sampled during the anesthetic consultation. The racial correction factor was not used because:

a) collecting statistics referring to racial or ethnic origin is forbidden in France and b) this correction factor only applies to African Americans.[22]

Population Study

Patients were included if they were ≥ 18 years-old,free from CKD at the time of surgery (*i.e.* baseline eGFR above 60 mL/min/1.73m^2), and scheduled for elective (non urgent) cardiac surgery with CBP between 2005 and 2015. We excluded patients who had a prior history of cardiac surgery and those without available serum creatinine measurements within 7 days post-surgery.

AKI: Exposure Status, Recovery and CKD Outcome

For each patient we calculated the shift of serum creatinine values in the first 7 days following surgery. The AKI group was defined according to the KDIGO criteria,[1] by a 1.5-fold increase in baseline serum creatinine concentration within the first 7 days after surgery or by an increase greater than or equal to 0.3 mg/dL within 48 hours. This included all patients who needed renal replacement therapy during their stay. By definition, the recovering status was defined, in all patients, by an eGFR ≥ 90% the baseline and ≥ 60 mL/min/1.73m^2 between days 7 and 90 following surgery. 'Time to recovery' was the time from surgery to recovery during the period 7-90 days post-surgery. In the case of patients requiring dialysis, their recovery was manually checked by reviewing medical charts.

CKD was defined by at least two eGFR values less than or equal to 60 mL/min/1.73m^2 separated by an interval of at least 90 days.[1]Each CKD status and time was manually checked by looking at the raw data. 'Time to CKD' was defined as the period spent from time to recovery to the first occurrence of eGFR ≤ 60 mL/min/1.73m^2. The 10th percentile time to CKD was the time during which 10% of the patients developed CKD. For AKI-free patients, we decided that time would count from the moment they had an eGFR measured during the recovery period (7-90 POD), similar to their match.

Data Sources

The study was completed using 2 independent blinded databases from each hospital. Clinical research associates prospectively input all clinical data from the study into these databases. These bases were automatically updated with all serum creatinine levels measured for each patient during the study period. The rate of missing data is presented in Supplemental Digital Content 1. All the data were analyzed and anonymized in a blinded manner. As requested by law, these two databases were officially reported to the Commission nationale de l'informatique et des libertés (CNIL), the French Data Protection Authority.

Statistical Analyses

Continuous variables for individuals with and without AKI were expressed as mean ±Standard Deviation (SD) or as median 25^{th}–75^{th} percentile for non-normally distributed variables, or number and percentage. Unmatched data were analyzed using the Mann-Whitney or student t test. Cumulative incidence curves were calculated with Kaplan Meier methods and compared using the log-rank test. Incidence rates were calculated and compared using Poisson regression adjusted on propensity score.

A propensity score for AKI was estimated using the following covariates: age, body mass index, pre-operative eGFR, clamping time and extracorporeal circulation, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), left ventricular ejection fraction (LVEF), type of surgery. The variables included in the propensity score model were selected among available baseline variables based on known associations between CKD and AKI[23] with a non-parsimonious logistic regression. This score was used to match each patient developing AKI to one control with a similar logit of the propensity score based on nearest neighbor matching without replacement using calipers of width equal to 0.2 SD.[24,25]An

absolute standardized difference less than 10% was considered to support the assumption of balance between groups.[26]

The matching was followed by a Cox regression analysis stratified for matched pairs. Survival analyses were performed until September 2015. For the CKD endpoint, each patient was censored at the end of the study period, *i.e.* at the time of the last available eGFR. We ensured that our Cox model met the proportional hazard assumption.[27]Because the matching process was without replacement and to assess reliability, we used bootstrapping re-sampling and presented all the results as mean values [95% confidence interval (CI)].[28]

Since the assumption of independence could not be verified, the drop-out subjects could be different between CKD and non-CKD patients. This informative censoring might have introduced a bias in our results, so we therefore performed an inverse probability of censoring weighted (IPCW) Cox regression in order to take such a bias into account.[29] Last, to assess the potential effect of unmeasured confounders, we conducted a Rosenbaum bounds sensitivity analysis.[30] This analysis estimates the magnitude of a hidden residual bias that would have to be present to explain the associations actually observed.

A p value of less than 0.05 was considered significant, and all p values were two tailed. Statistical analyses were performed using R software.

RESULTS

Baseline Population

Of the 7471 patients screened, we identified 4791 participants who met the inclusion criteria. We then excluded 2030 patients because they don't have sufficient follow up. From this cohort, 1375 (29%) developed AKI and 685 (50%) fully recovered their renal function (**Figure 1**). As expected, in the whole population study (*i.e.* before the matching of AKI patients with non-AKI patients according to the propensity score) some of the variables were

significantly different between the two groups (**Table 1**).

Bootstrapped Matched Cohort

Among the 685 patients who had fully recovered from AKI whose propensity score was available, 597 were successfully matched to a control patient. None of the variables associated with AKI and used in the propensity score differed significantly between AKI and non-AKI patients after matching (**Table 1& Figure 2)**. The median number of serum creatinine measurements during the follow-up period was 16 (11–28) and 11 (8–16) for the AKI and control groups respectively. The characteristics of the 61 patients who could not be matched because the propensity score could not be calculated (due to missing data) are shown in Supplemental Digital Content 2.

CKD Outcome in AKI and Non-AKI Patients

In the matched cohort, 34 out of the 597 patients who fully recovered from AKI developed CKD during the follow-up period, as opposed to 17 of the control patients **(Figure 3)**. The median 10^{th} percentile time to the diagnosis of CKD in those experiencing AKI was 159 days, as opposed to 594 days in the control group. Thus, incident rates for CKD were 15.7 and 5.1/100 person years in the AKI and control groups, respectively (p=0.0007 ; **Table 2**). The matched cohort hazard ratio (HR) for the development of stage 3 CKD was significantly higher in the AKI group (HR=2.3; bootstrapping 95%CI= [1.9–2.6]). It did not differ from the HR calculated from the IPCW Cox regression (HR=2.5; 95%CI= [1.6–4.1])

Impact of "Threshold Effect"

Arbitrarily using a ≥25% decrease in eGFR as another marker for significant deterioration of renal function, HR was still significantly increased after a transient episode of AKI (HR=2.2, 95%CI= [1.4–3.2]).

Impact of Severity of AKI

Regardless of AKI severity, HR for CKD was still significantly increased after a resolving episode of AKI, respectively 2.3 [1.8–2.6] for AKI stage 1 and 11 [6-12] for AKI stages 2 and 3.

Sensitivity Analyses

We used a sensitivity analysis with Rosenbaum bounds to assess the potential effect of unmeasured confounders. Rosenbaum bounds suggested a γ value of 1.4. This means that for any unmeasured confounder that would explain a higher rate of CKD in the AKI population, the confounder would need to produce a 40% increase in the odds of undergoing AKI.

DISCUSSION

Our study demonstrates that CKD-free adult patients developing AKI following elective cardiac surgery with CBP, and then fully recovering from AKI, are at increased risk of acquired stage 3 CKD or worse when compared to a similarly exposed, AKI-free population of patients. As in several other studies published previously, this risk is high very early and CKD typically occurs within weeks post-surgery.[2,7,11,31] Since baseline eGFR was well balanced between AKI and AKI-free patients, this study found that risk was not dependent on baseline renal function.

In our view, these data firmly consolidate the recent paradigm shift regarding the delayed outcome of AKI, because of five methodological aspects inherent to the design of our study: 1) first, we purposely selected for study a unique and homogeneous circumstance where AKI was a risk; 2) we created and validated a propensity score for the development of AKI and this allowed us to match every AKI patient with a control, which further reduced biases (in particular, AKI and non-AKI patients had similar age, pre-operative eGFR, LVEF and EuroSCORE, and they underwent similar extracorporeal circulation and clamping times); 3)

we did not use a diagnostic code system, but used numerical values of serum creatinine and estimated values of GFR to identify AKI or CKD: thus, whether acute or chronic, any alteration of renal function was defined by objective biological values; 4) we included all stages of AKI according to the sensitive and universal KDIGO criteria; 5) most importantly, we deliberately excluded patients who had not recovered their baseline renal function and matched the patients according to their post-operative eGFR .

Previous studies have strongly suggested a link between the occurrence of AKI and the development of CKD. Amdur *et al.* reported an adjusted HR of 4 following an acute "tubular necrosis" or "renal failure" (using diagnostic codes) occurring in patients without pre-existent CKD.[17]Ishani*et al.* found an adjusted HR of 13 for a code of end stage renal disease (ESRD) after acute kidney injury.[9]Lastly, Wald *et al.*, focusing on patients admitted to an intensive care unit and developing an AKI episode requiring renal replacement therapy, reported an adjusted HR of 3.2 for the risk of developing CKD and necessitating dialysis.[6]It has to be noted that the risk of CKD occurs particularly early. Likewise, in 2011, based on eGFR values obtained following cardiac surgery, Ishani *et al.* noted that AKI defined by an increase of 25% to 49% in serum creatinine *vs* baseline in the first 7 days resulted in a HR of 4 as early as 3 months post-surgery.[2] In the most recently published study concerning the risk of AKI following cardiac surgery, HR for ESRD (identified by a diagnostic code) was 6.2 in patients with normal pre-operative renal function.[31]Phenotyping these patients will be important so as to understand the etiology of such a rapid deterioration of renal function, in particular the characterization of urine (ions, quantity and type of proteinuria, and sediment). Since it is not known that an episode of AKI impairs *heart* recovery after cardiac surgery, and since AKI-triggered CKD has been reported to be severe enough to potentially result in ESRD, we are probably looking at parenchymal, not pre-renal, renal failure.

The biological mechanism(s) by which AKI precipitates the occurrence of CKD are being extensively studied. Despite efforts to match the AKI population with controls theoretically similarly prone to develop AKI/CKD, we may not rule out the possibility that the mean renal reserve is lower in the global AKI population,[32] since screening of renal reserve is not routinely conducted prior to cardiac surgery. In further exploratory studies, amino-acid loading could be considered before the scheduled circumstances which put patients at risk of AKI, in order to test the hypothesis that an episode of AKI often merely reflects a nephron loss, low enough to escape detection using serum creatinine measures when patients are exposed to a hemodynamic challenge, but high enough to induce AKI according to the most recent definition. Although this possibility seems likely (because the incidence of CKD occurs rapidly), the risk of AKI-induced CKD is similarly increased in the elderly and in children, which suggests that other mechanisms are also involved.[33,34]

Thus, although AKI resolves functionally within days or weeks, it may yet have triggered a strong pro-fibrotic response, resulting in accelerated scarring of the kidneys. In the last five years, experimental studies have indeed documented what is now called a "maladaptive" repair. To name only a few of the mechanisms potentially at stake in mammals, it was found that even a transient episode of AKI could result in:a) an incapacity for tubular epithelial cells to resume normal production of energy;[12]b) a cell cycle arrest or delay;[14]and c) a reprogramming of myofibroblasts through the epigenetic silencing of *RASAL1*, a gene encoding a potent inhibitor of cell proliferation.[13]The latter, however, was reported as not occurring in the ischemic model of AKI. In sum, some patients with supposedly pristine kidneys might still evolve towards CKD *because of* (not only *after*) an episode of AKI.

Interestingly, we found a high incidence of CKD stage 3 in the group without AKI. This incidence is largely superior to that seen in the general population (respectively 51000 and 5000 per million person yearsfor *de novo* CKD[35]).

In the case of cardiac surgery, AKI defined using the KDIGO criteria may only reflect the renal consequences of various injuries such as extra corporeal circulation or arterial clamping. These injuries probably act as a continuum limiting the traditional definition of AKI. A study addressing the impact of extra corporeal circulation *per se* on renal outcome long-term is needed.

Our study has some limitations: 1) retrospective by nature, we may not exclude the possibility that an additional AKI occurred, or that drugs interfering with glomerular filtration were introduced during the observation period. In any case, we believe there are sufficient data in the literature to require that patients developing AKI and recovering from it, are put under close scrutiny; 2) The French law demands a "color-blind" model of data collection, which means that we did not apply the GFR-correcting factor for black patients. Nevertheless, the proportion of African-Americans in the population is small in France, and un our study, serum creatinine was assessed for each individual relative to his/her own baseline serum creatinine; 3) we censored our patients at the time of the last serum creatinine measurement available to avoid information bias caused by insufficient creatinine values (and thereby considering a patient CKD free where he is not), so the additional bias linked to informative censoring was therefore tested by IPCW Cox regression; 4) One month after the surgery, there was no scheduled patient follow-up. Thus, the number of serum creatinine measurement differs between the patients developing AKI and their control. Nevertheless the median duration of follow up was the same. In the Supplemental Digital Content 3 we present the time distribution of GFR estimation according to their AKI status. 5) for patients who required a blood transfusion in the perioperative period, the number of packed red cells was not available; 6) the existence of a residual confounding factor is not impossible because the scope of measured confounders is limited. However, to assess this risk we performed a Rosenbaum bounds sensitivity analysis, allowing us to estimate the likelihood that an

unknown confounder could explain the observed differences in CKD. A γ value of 1.4 between AKI and control patients, however, suggests that it is unlikely.

These findings tackle the issue of potential nephrologist follow-up after AKI even if the patient has totally recovered renal function. The value of specialist follow-up after hospitalization for an array of acute conditions is well established in terms of mortality and rehospitalization.[36-38]While it is estimated that 76% of patients surviving a myocardial infarction are followed by cardiologists, it is still not our routine practice to recommend that renal function of patients who fully recovered from an AKI be monitored in the following weeks or months.[39]For those experiencing a rapid decline in renal function, interventional studies – yet to be designed – are undoubtedly needed.

In summary, regardless of its severity, a fully recovering episode of AKI following cardiac surgery in patients without pre-existing CKD is strongly associated with a subsequent increase in the risk of *de novo* CKD. Complementary research is required to understand the biological mechanisms involved, and to invent new therapeutic approaches.

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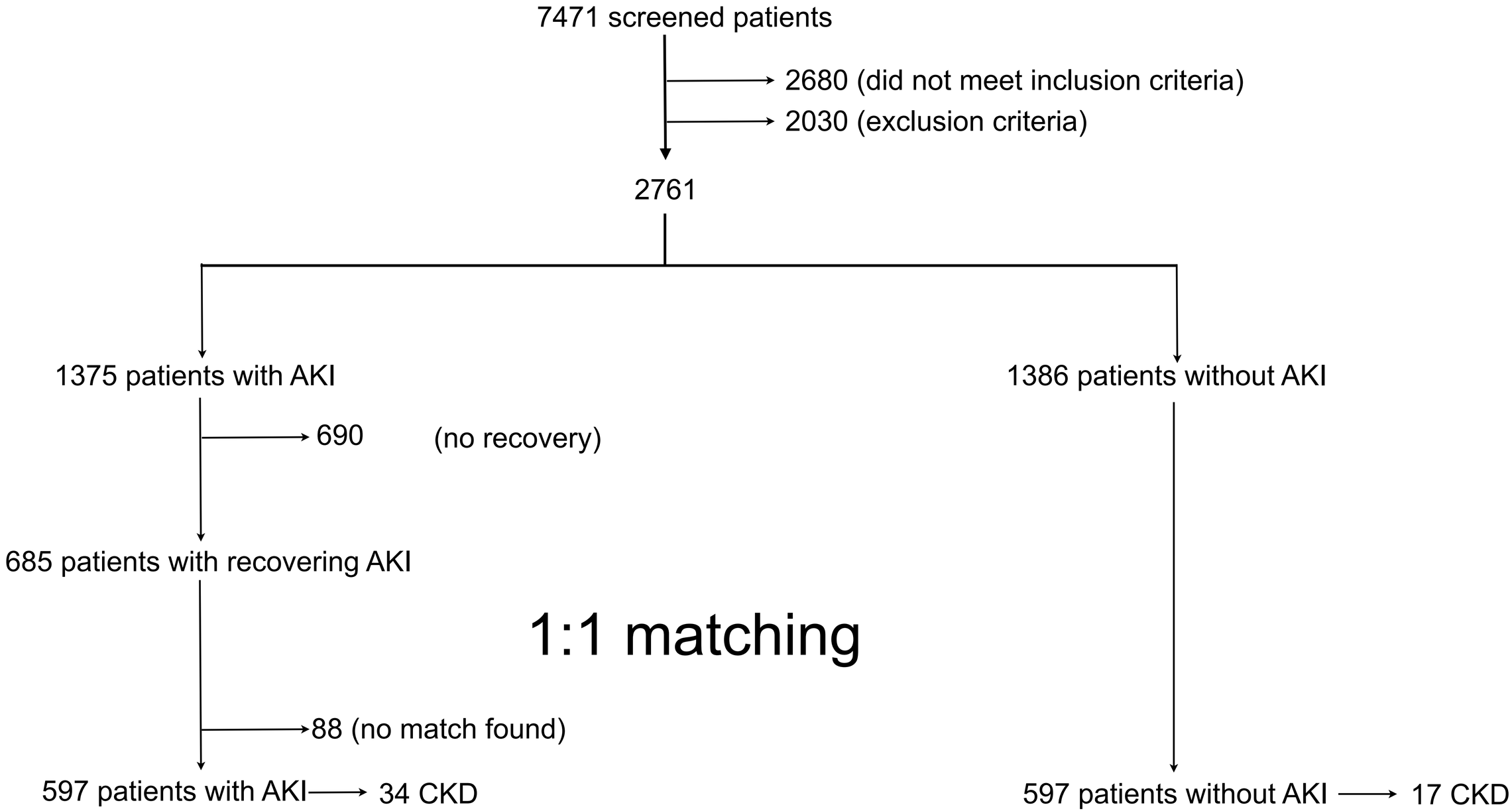
Figure 1: Study flow chart

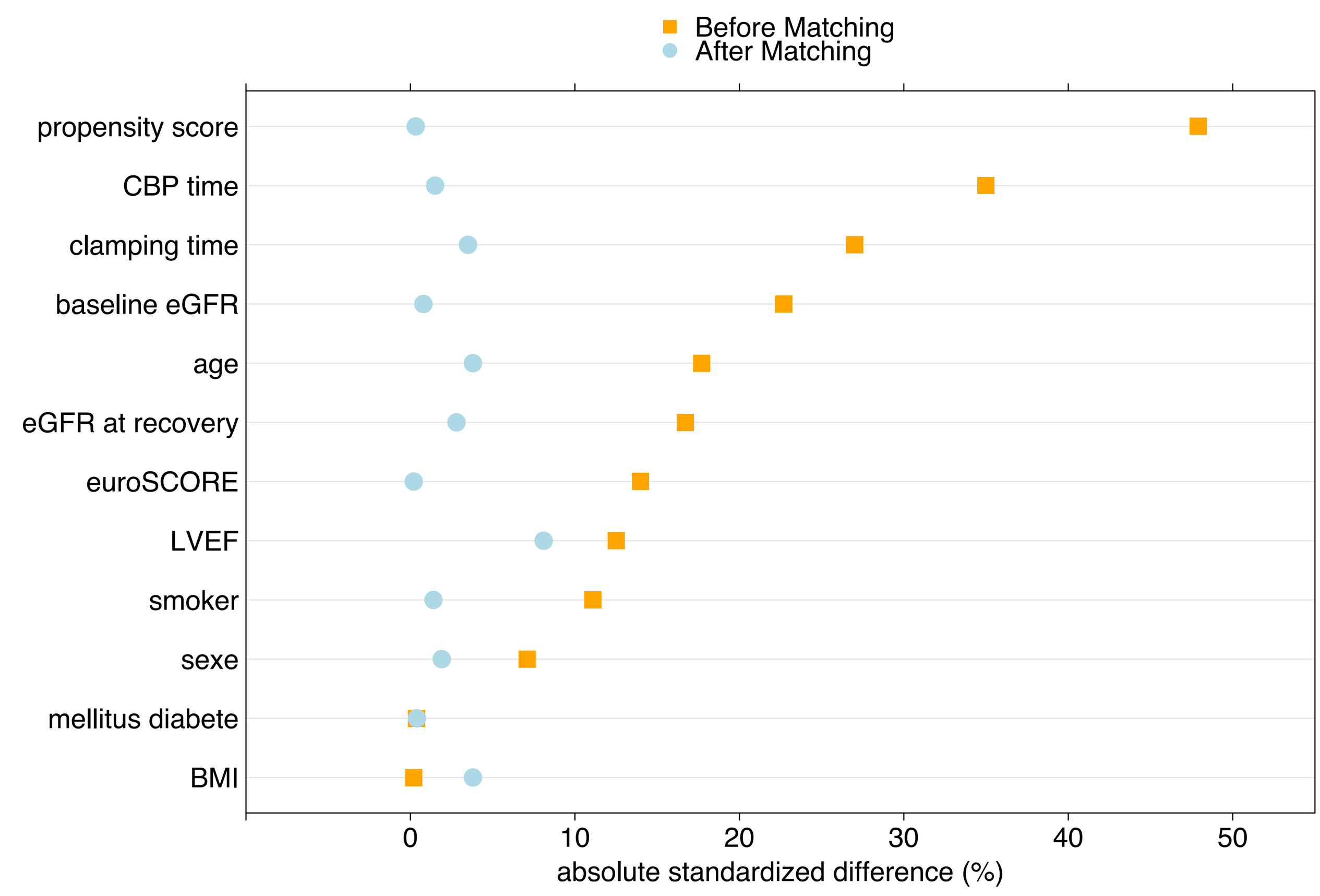
Figure 2: Baseline covariates absolute standardized differences used in the propensity score, before and after matching process.

Figure 3: Kaplan Meier curve of CKD by exposure status (recovered AKI group vs. controls) among matched cohort patients.

Table 1: Patient characteristics of cohort, before and after matching (SdD: Standardized difference), developing or not developing AKI.

Table 2: Cumulative incidence risk and hazard ratios for CKD by AKI status among matched cohort (p-value computed from incidence rate ratio using Poisson regression).


7471 screened patients
2680 (did not meet inclusion criteria)
2030 (exclusion criteria)
2761
1375 patients with AKI
1386 patients without AKI
690
(no recovery)
685 patients with recovering AKI
1:1 matching
88 (no match found)
597 patients with AKI
34 CKD
597 patients without AKI
17 CKD


Before Matching
After Matching
propensity score
CBP time
clamping time
baseline eGFR
age
eGFR at recovery
euroSCORE
LVEF
smoker
sexe
mellitus diabete
BMI
0
10
20
30
40
50
absolute standardized difference (%)

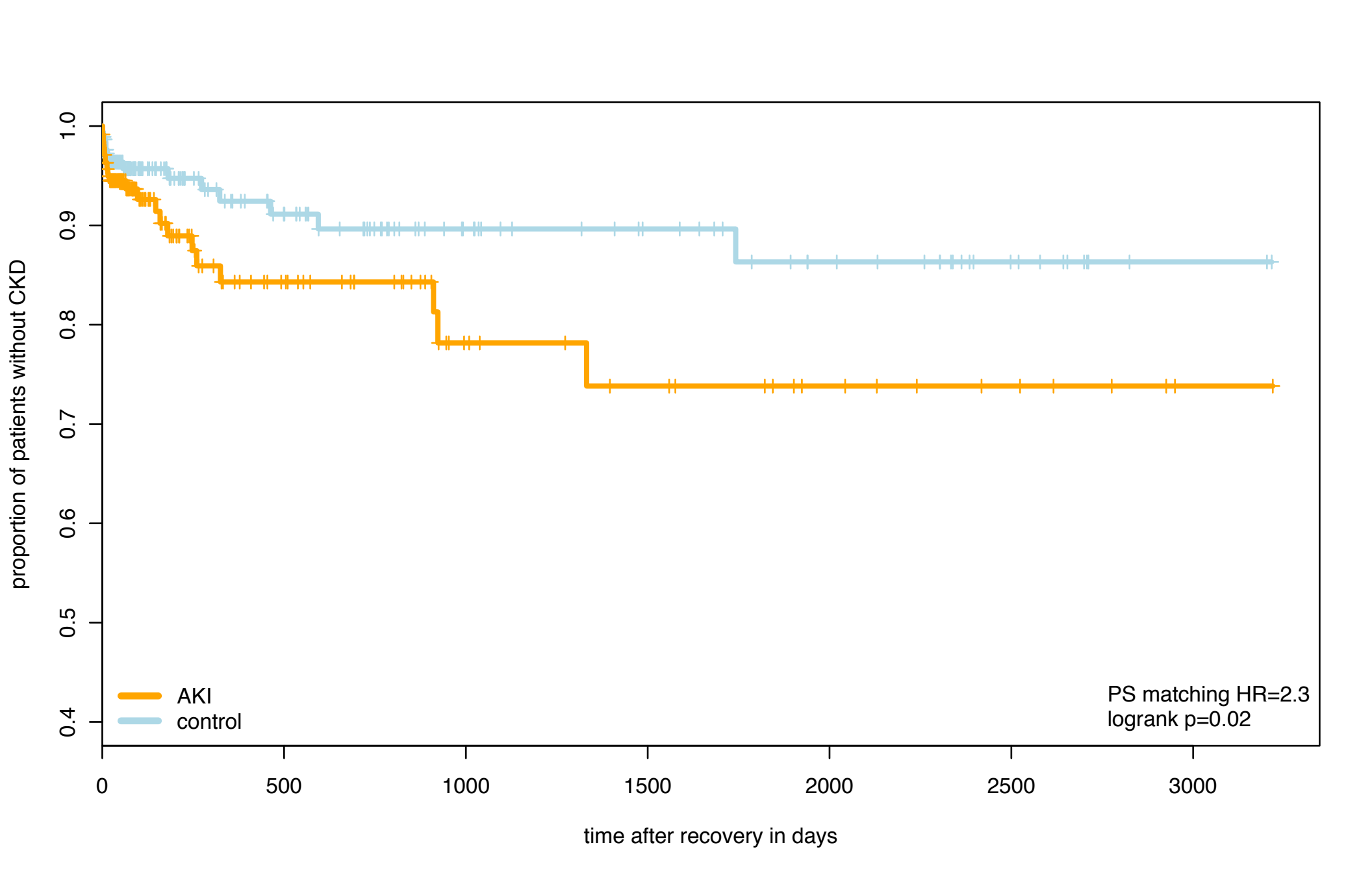

proportion of patients without CKD
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0
500
1000
1500
2000
2500
3000
time after recovery in days
AKI
control
PS matching HR=2.3
logrank p=0.02

Table 1

	Unmatched cohort				Matched cohort		
	AKI (n=1375)	CTRL (n=1385)	P value	SdD (%)	AKI (n=597)	CTRL (n=597)	SdD (%)
Propensity score - mean	0.38	0.30	<0.0001	*47.9*	0.34	0.34	0.32
Baseline eGFR (mL/min/1.73m^2)- mean	79	82	<0.0001	*22.7*	79	79	0.79
eGFR at recovery (mL/min/1.73m^2)- mean	91	95	0.0004	*16.7*	91	92	2.8
Age (years) - mean	66	64	<0.0001	*17.7*	66	66	3.8
EuroSCORE (%) - mean	4.6	3.7	0.001	*14.0*	4.3	4.3	0.2
BMI - mean	26.6	26.6	0.97	0.2	26.7	26.9	3.8
CBP time (min) - mean	90	71	<0.0001	*35*	78	79	1.5
Clamping time (min) - mean	64	54	<0.0001	*27*	58	59	3.5
Male - %	72	69	0.1	7.1	72	71	1.9
LVEF (%) - mean	56	57	0.007	*12.5*	55	56	8.1
Smoker - %	15	19	0.02	*11.1*	16	16	1.4
diabetes mellitus - %	24	24	0.93	*0.38*	25	25	0.39

Table 2

	No of CKD	HR for CKD Mean [95%CI]	Incidence rate
With AKI (n=597)	34	2.3 [1.9-2.6]	15.7
Without AKI (n=597)	17	1 (ref)	5.1*