Elevated BP after AKI

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ABSTRACT

The connection between AKI and BP elevation is unclear. We conducted a retrospective cohort study to evaluate whether AKI in the hospital is independently associated with BP elevation during the first 2 years after discharge among previously normotensive adults. We studied adult members of Kaiser Permanente Northern California, a large integrated health care delivery system, who were hospitalized between 2008 and 2011, had available preadmission serum creatinine and BP measures, and were not known to be hypertensive or have BP>140/90 mmHg. Among 43,611 eligible patients, 2451 experienced AKI defined using observed changes in serum creatinine concentration measured during hospitalization. Survivors of AKI were more likely than those without AKI to have elevated BP—defined as documented BP>140/90 mmHg measured during an ambulatory, nonemergency department visit—during follow-up (46.1% versus 41.2% at 730 days; $P<0.001$). This difference was evident within the first 180 days (30.6% versus 23.1%; $P<0.001$). In multivariable models, AKI was independently associated with a 22% (95% confidence interval, 12% to 33%) increase in the odds of developing elevated BP during follow-up, with higher adjusted odds with more severe AKI. Results were similar in sensitivity analyses when elevated BP was defined as having at least two BP readings of >140/90 mmHg or those with evidence of CKD were excluded. We conclude that AKI is an independent risk factor for subsequent development of elevated BP. Preventing AKI during a hospitalization may have clinical and public health benefits beyond the immediate hospitalization.

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Elevated BP is a leading risk factor for global disease burden.[1,2] There is a graded relation between level of BP and risk of cardiovascular disease and death. Worldwide, about 13.5% of premature deaths, 54% of strokes, and 47% of ischemic heart disease events have been attributable to high BP.[3] Numerous animal models support the hypothesis proposed by Guyton[4] decades ago that the kidneys have a critical role in determining chronic level of BP.[5] Consistent with this, all of the Mendelian inherited disorders of hypertension identified to date in humans can be related to abnormalities in renal salt handling.[6,7]

Animal models of renal ischemia-reperfusion injury have shown that postischemic rats develop salt-sensitive hypertension, potentially mediated through alterations in pressure natriuresis.[8,9] Some prior studies in pediatric patients had suggested higher rates of developing hypertension among children who had recovered from various forms of acute renal disease (such as hemolytic uremic syndrome or GN).[10–12]

We investigated whether an episode of AKI is an independent risk factor for subsequent elevation in BP among a large community–based population of adult patients who were hospitalized.

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RESULTS

Baseline Characteristics

In total, 43,611 eligible patients were identified between 2008 and 2011 (Figure 1). Characteristics of the cohort at the time of the first qualifying hospitalization during the study period are shown in Table 1. Mean age was 56 years old, and nearly 60% were women; there was also broad racial/ethnic diversity (Table 1). Median preadmission BP (using the most recent outpatient, nonemergency department BP reading from before hospitalization) was 120/72 mmHg.

During their index hospitalizations, 2451 patients experienced AKI, and 41,160 patients did not. Those who had AKI were older, more likely to be men and black, and more likely have diabetes mellitus and heart failure (Table 1). Preadmission baseline eGFR was preserved for both groups. Only a small fraction of patients had eGFR<60 ml/min per 1.73m^2, although this was more common among those who had AKI versus those who did not have AKI (5% versus 0.7%, respectively; $P<0.001$). Among patients who had AKI, 1741 (71.0%) patients were classified as stage 1, 374 (15.3%) patients were classified as stage 2, and 336 (13.7%) patients were classified as stage 3 (including 58 patients who required acute dialysis).

AKI Status and Subsequent BP Elevation

During the subsequent 2 years, the median number of BP measurements for patients with AKI was 11 (interquartile range [IQR]=5–23) and patients who did not have AKI was 9 (5–19). By 180 days posthospital discharge, the vast majority had at least one BP measured in the outpatient setting in both groups (Table 2). Survivors of AKI were more likely to have elevated BP during follow-up (Figure 2). For example, at 730 days, 46.1% of survivors of an AKI hospitalization had a documented systolic BP>140 mmHg and/or diastolic BP>90 mmHg versus 41.2% of survivors of a non-AKI hospitalization ($P<0.001$). After adjustment for potential confounders, including demographics, body mass index, most recent preadmission ambulatory BP, smoking status, diabetes mellitus, chronic heart failure, coronary heart disease, most recent preadmission ambulatory eGFR, and history of proteinuria, AKI was still associated with a 22% (95% confidence interval [95% CI], 12% to 33%) increased odds of developing an elevated BP during follow-up (Table 2).

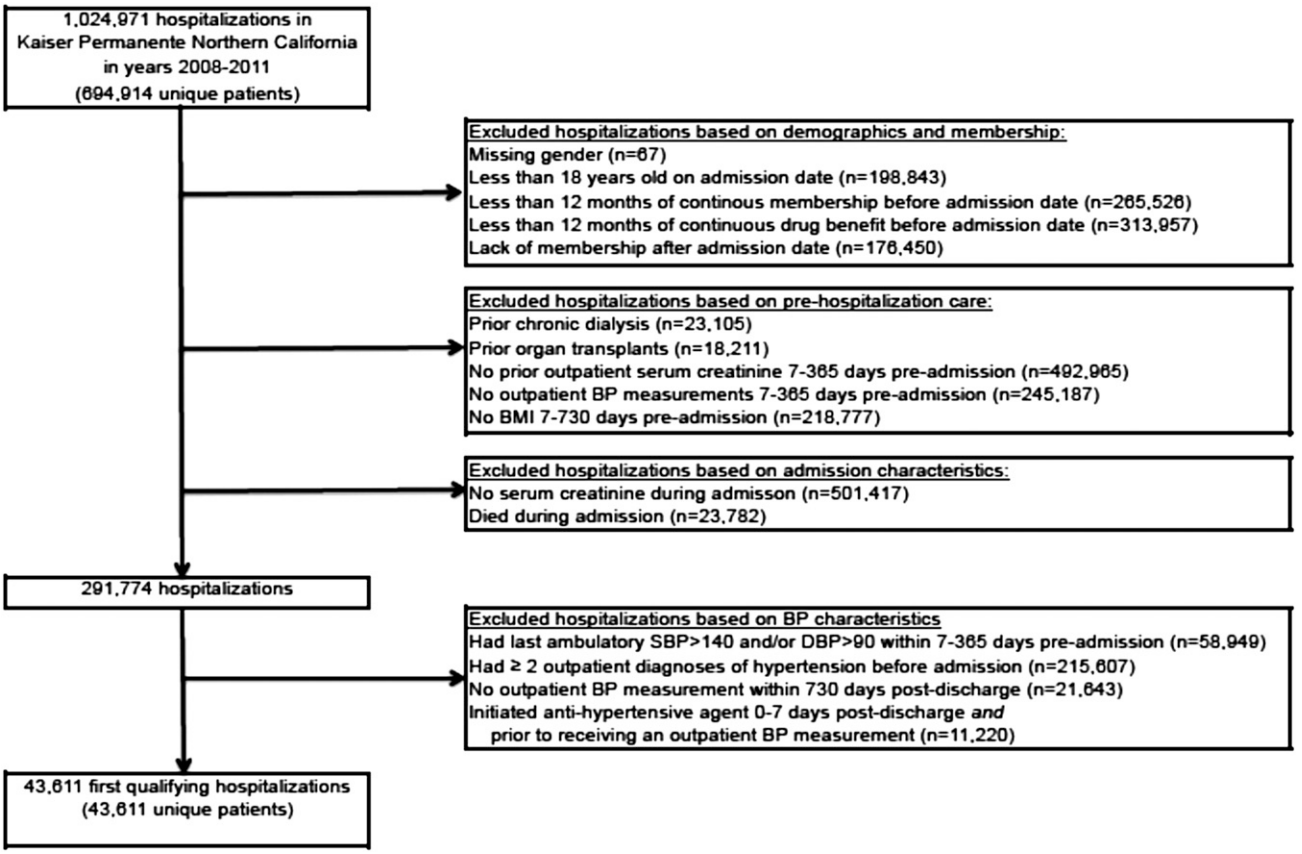

Figure 1. Assembly of an analytic cohort of patients who were hospitalized between January 1, 2008, and December 31, 2011. After applying a series of exclusion criteria which are not mutually exclusive, 43,611 unique patients were identified for our main analysis. BMI, body mass index; DBP, diastolic BP; SBP, systolic BP.

Table 1. Patient characteristics in AKI versus non-AKI groups

Variable	Overall (*n*=43,611)	AKI (*n*=2451)	No AKI (*n*=41,160)	*P* Value
Demographic characteristics				
Age, yr				
Mean (SD)	56.1 (17.3)	57.7 (18.5)	56.0 (17.2)	<0.001
Median (IQR)	56.8 (43.5–68.5)	59.0 (44.2–72.0)	56.7 (43.5–68.3)	<0.001
Range	18.0–110.3	18.0–99.4	18.0–110.3	
Women, *N* (%)	25,991 (59.6)	1214 (49.5)	24,777 (60.2)	<0.001
Race, *N* (%)				<0.01
White	35,087 (80.5)	1928 (78.7)	33,159 (80.6)	
Black	2769 (6.3)	200 (8.2)	2569 (6.2)	
Asian	4979 (11.4)	280 (11.4)	4699 (11.4)	
Other/missing	776 (1.8)	43 (1.8)	733 (1.8)	
Hispanic ethnicity, *N* (%)	7045 (16.2)	393 (16.0)	6652 (16.2)	0.87
Body mass index, kg/m^2				
Mean (SD)	28.1 (7.1)	28.8 (7.6)	28.1 (7.0)	<0.001
Median (IQR)	27.0 (23.5–31.4)	27.5 (23.8–32.2)	27.0 (23.5–31.3)	<0.001
Categories, *N* (%)				<0.001
<18.5	1284 (2.9)	78 (3.2)	1206 (2.9)	
18.5–24.99	13,920 (31.9)	728 (29.7)	13,192 (32.1)	
25.0–29.99	14,535 (33.3)	763 (31.1)	13,772 (33.5)	
≥30	13,872 (31.8)	882 (36.0)	12,990 (31.6)	
Most recent ambulatory BP, mmHg				
Systolic BP				
Mean (SD)	119.5 (12.2)	118.8 (13.1)	119.6 (12.1)	<0.01
Median (IQR)	120.0 (111.0–129.0)	120.0 (110.0–129.0)	120.0 (111.0–129.0)	<0.05
Diastolic BP				
Mean (SD)	71.6 (9.3)	70.5 (9.9)	71.7 (9.2)	<0.001
Median (IQR)	72.0 (65.0–79.0)	71.0 (64.0–78.0)	72.0 (66.0–79.0)	<0.001
Medical history, *N* (%)				
Current or former smoker	11,390 (26.1)	714 (29.1)	10,676 (25.9)	<0.001
Diabetes mellitus	2134 (4.9)	170 (6.9)	1964 (4.8)	<0.001
Chronic heart failure	523 (1.2)	93 (3.8)	430 (1.0)	<0.001
Coronary heart disease	1251 (2.9)	80 (3.3)	1171 (2.8)	0.23
Hospitalization characteristics, *N* (%)				
Intensive care unit stay	4757 (10.9)	561 (22.9)	4196 (10.2)	<0.001
AKI KDIGO Stages				
Stage 1	1741 (4.0)	1741 (71.0)	N/A	
Stage 2	374 (0.9)	374 (15.3)	N/A	
Stage 3	336 (0.8)	336 (13.7)	N/A	
Medications on admission, *N* (%)				
Diuretics	3159 (7.2)	429 (17.5)	2730 (6.6)	<0.001
β-Blockers	4874 (11.2)	397 (16.2)	4477 (10.9)	<0.001
Calcium channel blocker	456 (1.0)	43 (1.8)	413 (1.0)	<0.001
ACEI or angiotensin II receptor blocker	3431 (7.9)	389 (15.9)	3042 (7.4)	<0.001
Preadmission renal function measures				
Mean eGFR, ml/min per 1.73 m^2 (SD)	131.8 (24.1)	124.6 (34.1)	132.2 (23.3)	<0.001
Median eGFR, ml/min per 1.73 m^2 (IQR)	137.0 (116.9–148.6)	130.8 (101.9–149.0)	137.3 (117.3–148.5)	<0.001
eGFR<60 ml/min per 1.73 m^2, *N* (%)	408 (0.9)	123 (5.0)	285 (0.7)	<0.001
Presence of proteinuria, *N* (%)	7674 (17.6)	776 (31.7)	6898 (16.8)	<0.001

ACEI, angiotensin–converting enzyme inhibitor; N/A, not applicable.

This association between AKI and risk of a subsequent elevated BP seemed strongest shortly after hospitalization (adjusted odds ratio [OR], 1.40; 95% CI, 1.28 to 1.54 for the first 180 days after hospitalization) (Table 2).

Notably, more severe AKI was associated with higher odds of observing elevated BP. For example, across the entire follow-up period, the adjusted OR for stage 3 AKI was 1.82 (95% CI, 1.45 to 2.29), but the adjusted OR for stage 1 AKI was only 1.09 (95% CI, 0.96 to 1.21) (Table 3).

Table 4 shows the results of our five sensitivity analyses. In all five analyses, AKI was associated with higher adjusted odds of elevated BP after hospital discharge, and the degree of association

Table 2. Multivariable association of an episode of AKI on subsequent development of elevated BP after hospital discharge

	Period after Hospital Discharge (d)			
	180 (*n*=40,861)	365 (*n*=42,845)	540 (*n*=43,407)	730 (*n*=43,611)
No. of subjects with AKI	2367	2426	2438	2451
Unadjusted OR for elevated BP postdischarge,[a] AKI versus no AKI	1.41	1.35	1.27	1.22
95% CI	1.29 to 1.54	1.24 to 1.47	1.17 to 1.38	1.12 to 1.32
Adjusted[b] OR for elevated BP postdischarge,[a] AKI versus no AKI	1.40	1.36	1.27	1.22
95% CI	1.28 to 1.54	1.25 to 1.49	1.17 to 1.39	1.12 to 1.33

[a]Defined as systolic BP>140 mmHg and/or diastolic BP>90 mmHg during follow-up.
[b]Adjusted for age at index hospitalization, sex, race, body mass index, last ambulatory systolic and diastolic BP measurements, smoking status, diabetes mellitus, chronic heart failure, coronary heart disease, last ambulatory eGFR, and proteinuria.

remained strong and very similar in magnitude to our main analysis (Table 2). For example, exclusion of patients who had evidence of preexisting CKD (eGFR<60 ml/min per 1.73 m^2 or documented proteinuria) did not attenuate the adjusted odds of elevated BP for patients with AKI (Table 4, sensitivity analysis 2). The association between AKI and elevated BP was actually stronger when the outcome was changed to requiring at least two BP readings of >140/90 mmHg (Table 4, sensitivity analysis 3). When we reclassified patients who were originally labeled as having AKI solely because of a 0.3-mg/dl or greater difference between peak inpatient and baseline serum creatinine (without meeting at least 50% increase in serum creatinine) as no AKI, results were also similar (Table 4, sensitivity analysis 4).

DISCUSSION

Within a very large, diverse, and contemporary community–based population without prior hypertension, we found that an episode of AKI during hospitalization was an independent risk factor for subsequent development of BP elevation. This association was present within the first 180 days after hospital discharge and persisted throughout the first 2 years of follow-up. Our results were similar in multiple sensitivity analyses that excluded patients who were receiving medications that could affect BP or patients with clinically evident baseline CKD or required at least two temporally spaced measurements of elevated BP.

Our study contributes novel information in several ways. It adds to the list of potential adverse sequelae after an episode of AKI. Much of the literature to date has focused on the risk of death as well as initiation and acceleration of clinically evident CKD after AKI.[13–15] A recent study suggested that AKI may also increase risk of cardiovascular disease.[16] It is possible that one potential mechanism connecting AKI with cardiovascular events in the subsequent months to years after hospital discharge is through unfavorable hemodynamics, such as development of incident hypertension or worsening of preexisting

Table 3. Multivariable association of the severity of AKI on subsequent development of elevated BP after hospital discharge

	Period after Hospital Discharge (d)			
	180 (*n*=40,861)	365 (*n*=42,845)	540 (*n*=43,407)	730 (*n*=43,611)
No. of subjects with AKI				
Stage 1 AKI	1667	1721	1731	1741
Stage 2 AKI	367	372	373	374
Stage 3 AKI	333	333	334	336
Unadjusted OR for elevated BP postdischarge[a]				
Stage 1 AKI versus no AKI	1.23	1.2	1.13	1.09
95% CI	1.11 to 1.38	1.09 to 1.33	1.03 to 1.25	0.99 to 1.20
Stage 2 AKI versus no AKI	1.65	1.51	1.49	1.42
95% CI	1.33 to 2.05	1.23 to 1.86	1.22 to 1.83	1.16 to 1.75
Stage 3 AKI versus no AKI	2.18	2.13	1.88	1.81
95% CI	1.75 to 2.72	1.72 to 2.65	1.52 to 2.33	1.46 to 2.25
Adjusted[b] OR for elevated BP postdischarge[a]				
Stage 1 AKI versus no AKI	1.23	1.21	1.13	1.09
95% CI	1.10 to 1.37	1.09 to 1.34	1.02 to 1.26	0.98 to 1.21
Stage 2 AKI versus no AKI	1.66	1.53	1.51	1.45
95% CI	1.32 to 2.08	1.23 to 1.90	1.22 to 1.87	1.17 to 1.79
Stage 3 AKI versus no AKI	2.18	2.17	1.89	1.82
95% CI	1.74 to 2.74	1.73 to 2.71	1.52 to 2.37	1.45 to 2.29

[a]Defined as systolic BP>140 mmHg and/or diastolic BP>90 mmHg during follow-up.
[b]Adjusted for age at index hospitalization, sex, race, body mass index, last ambulatory systolic and diastolic BP measurements, smoking status, diabetes mellitus, chronic heart failure, coronary heart disease, last ambulatory eGFR, and proteinuria.

Table 4. Sensitivity analyses

	Period after Hospital Discharge (d)			
	180	365	540	730
Sensitivity analysis 1: Excluding patients who were receiving antihypertensive drugs[a] at the time of hospital admission				
n	32,351	34,060	34,563	34,754
No. of subjects with AKI	1557	1602	1611	1621
Adjusted[b] OR for elevated BP postdischarge,[c] AKI versus no AKI	1.39	1.36	1.28	1.22
95% CI	1.24 to 1.56	1.22 to 1.52	1.15 to 1.42	1.10 to 1.36
Sensitivity analysis 2: Excluding patients who had eGFR<60 ml/min per 1.73 m^2 or documented prior proteinuria before hospitalization				
n	33,277	35,023	35,518	35,690
No. of subjects with AKI	1547	1588	1596	1602
Adjusted[d] OR for elevated BP postdischarge,[c] AKI versus no AKI	1.48	1.38	1.29	1.20
95% CI	1.32 to 1.66	1.23 to 1.53	1.16 to 1.43	1.08 to 1.34
Sensitivity analysis 3: Outcome of elevated BP more strictly defined as ambulatory SBP >140 mmHg and/or ambulatory DBP >90 mmHg at two separate visits				
n	40,861	42,845	43,407	43,611
No. of subjects with AKI	2367	2426	2438	2451
Adjusted[b] OR for elevated BP postdischarge, AKI versus no AKI	1.73	1.55	1.47	1.45
95% CI	1.53 to 1.95	1.40 to 1.73	1.34 to 1.63	1.32 to 1.59
Sensitivity analysis 4: AKI defined only using (peak inpatient creatinine)/(baseline creatinine)≥1.5 and excluding patients who met AKI criteria solely because of (peak inpatient creatinine)−(baseline creatinine)≥0.3 mg/dl				
n	40,861	42,845	43,407	43,611
No. of subjects with AKI	1652	1686	1695	1704
Adjusted[b] OR for elevated BP postdischarge,[c] AKI versus no AKI	1.47	1.41	1.31	1.28
95% CI	1.32 to 1.64	1.27 to 1.57	1.19 to 1.46	1.15 to 1.41
Sensitivity analysis 5: Outcome of elevated BP defined as ambulatory SBP >140 mmHg and/or ambulatory DBP >90 mmHg during follow-up after excluding all BP values during the first 90 d postdischarge				
n	26,922	36,937	39,539	40,340
No. of subjects with AKI	1575	2009	2111	2153
Adjusted[b] OR for elevated BP postdischarge, AKI versus no AKI	1.37	1.35	1.28	1.24
95% CI	1.21 to 1.56	1.22 to 1.50	1.17 to 1.41	1.13 to 1.36

SBP, systolic BP; DBP, diastolic BP.
[a]Antihypertensive drugs included here are diuretics, β-blockers, calcium channel blockers, angiotensin–converting enzyme inhibitors, and angiotensin II receptor blockers.
[b]Adjusted for age at index hospitalization, sex, race, body mass index, last ambulatory systolic and diastolic BP measurements, smoking status, diabetes mellitus, chronic heart failure, coronary heart disease, last ambulatory eGFR, and proteinuria.
[c]Defined as systolic BP>140 mmHg and/or diastolic BP>90 mmHg during follow-up.
[d]Adjusted for age at index hospitalization, sex, race, body mass index, last ambulatory systolic and diastolic BP measurements, smoking status, diabetes mellitus, chronic heart failure, coronary heart disease, and last ambulatory eGFR.

hypertension.[17] Our results extend previous findings in children regarding risk of hypertension after various forms of acute renal disease.[10–12] To our knowledge, this is the first study to examine this potentially important connection in adults. These data support calls for closer follow-up of patients after an episode AKI so that appropriate interventions can be implemented in a timely manner.[18]

Our results are physiologically plausible given the hypothesis by Guyton,[4] which motivated our investigation of the relation between AKI and subsequent BP level.[5] There exists some controversy in the current literature about whether mild to moderate AKI is causally related to any subsequent observed development or acceleration of CKD (or whether the association is caused by confounding by risk factors predisposing to both AKI and CKD).[19,20] However, a clinically evident decrease in eGFR after AKI may be a relatively advanced manifestation of residual damage. Total GFR can be an insensitive measure of parenchymal injury because of an adaptive increase in single-nephron GFR after recovery from AKI.[21] BP elevation may reflect more subtle renal injury that is important but not detectable by changes in serum creatinine concentration.

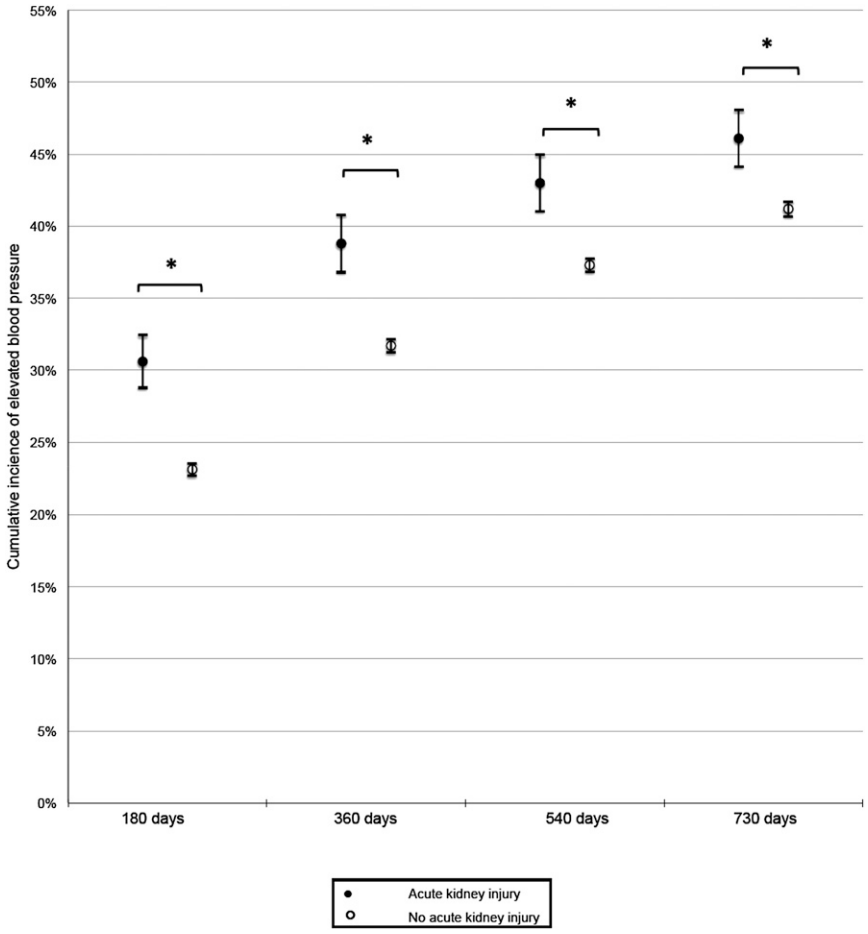

Figure 2. Cumulative incidence of elevated BP (systolic BP>140 mmHg and/or diastolic BP>90 mmHg) during the first 2 years after discharge among patients with and without AKI. Patients who had AKI had higher cumulative incidence of elevated BP at 180 days, 360 days, 540 days, and 730 days after discharge, compared with patients who did not have AKI. Error bars represent 95% CIs. *$P<0.05$.

At the same time, our study also contributes to the literature by identifying a potentially hitherto underappreciated cause of BP elevation. Most patients with hypertension are deemed essential, although there are some well known risk factors, such as older age and excess weight. Genetic studies have been less successful in explaining variations in the level of BP outside of the setting of rare Mendelian diseases,[22] and therefore, identifying potentially modifiable precursors of high BP is important. Recent studies show that on the order of 10% of hospitalizations are complicated by AKI defined by similar criteria to what we have used here[23,24] and that disease incidence seems to be increasing over time.[25–27] Thus, our findings may have substantial clinical and public health implications.

Prior studies have shown that the incidence of AKI can be reduced by measures, including isotonic intravenous fluid infusion before iodinated contrast administration,[28] off– versus on–pump coronary artery bypass surgery,[29] and potentially, real-time detection of incipient acute worsening of renal function[30] as well as early inpatient nephrology consultation.[31] If the AKI-BP elevation association is causal, then reducing the risk of AKI may not only reduce mortality and morbidity in the short term but also, confer large long–term public health benefits.

The strengths of this study include the plausibility of the physiologic connection and analysis of a contemporary, large community–based population with broad diversity across age, sex, and race/ethnicity. In addition, we used actual BP readings during follow-up to define the outcome rather than administrative diagnostic codes regarding hypertension. We also defined AKI on the basis of change in serum creatinine concentration rather than relying on administrative diagnostic codes, which are known to have suboptimal operating characteristics.[32] We leveraged a comprehensive electronic medical record to identify important covariates, including body mass index and diabetes mellitus. We carefully controlled for a wide range of potential confounders. We conducted several sensitivity analyses to ensure the robustness of our findings. Our results are also further supported by the stepwise association between more severe AKI and higher odds of developing an elevated BP during follow-up, which was even stronger when requiring a more stringent definition of elevated BP.

One limitation is that, because this was an observational study, association does not prove causality. It would be unethical to randomly assign patients to develop AKI or not and follow subsequent BP levels. Even in studies in which patients can be randomly assigned to interventions that reduce the risk of AKI, many of those patients likely will have prevalent hypertension (or be on medications that affect BP), and therefore, interpretation of subsequent BP levels would be extremely difficult. We did not have accurate information on urine output and therefore, were not able to use this parameter to classify AKI. Because this study is on the basis of data collected as part of routine clinical care, we were unable to ascertain BP levels at specific time points (*e.g.*, 90 days after AKI). Because we did not require a 48-hour window for the increase in serum creatinine of $\geq$0.3 mg/dl for our primary definition of AKI, we did not adopt the Kidney Disease Improving Global Outcomes (KDIGO) criteria strictly. However, our sensitivity analyses reveal that our conclusions are robust to nuanced differences in AKI definition. Although we are missing information on other potential risk factors for incident hypertension, such as family history, those factors are not known to increase risk of AKI. Similarly, there are no data that established causes of AKI, such as sepsis, result in a

subsequent increase in BP level after hospital discharge. The likelihood that our results are caused by residual confounding is reduced by the multiple experimental studies showing plausible pathophysiologic pathways connecting AKI to subsequent parenchymal renal damage and elevated BP.[4,5,8,9,33–36]

To enhance internal validity, we did implement several design decisions as detailed above, recognizing that they may affect generalizability. We excluded patients who had prevalent hypertension at baseline. Although it is plausible that AKI would exacerbate preexisting hypertension, we reasoned that it would be very difficult to detect such a signal, even if it existed, in patients with preexisting hypertension given that medication choices, dose changes, and associated changes in BP would make it very challenging to accurately detect an effect in an observational study. We could only study patients who had BP measured before and after hospitalization as part of routine clinical care. Both AKI and non-AKI groups had high numbers of postdischarge BP measurements (AKI group median =11 [IQR=5–23]; non–AKI group median =9 [IQR=5–19]), thus affording ample opportunities to detect elevated BP in both groups and rendering significant ascertainment bias unlikely. Because mortality was substantially higher in patients with AKI during follow-up (17.5% versus 8.8% by 730 days), there would actually be less observation time and opportunity to develop elevated BP. Thus, our observed estimates are likely to be conservative.

Although the majority of study participants had a urine dipstick in the 4 years before their index hospitalizations (82%), patients without urine dipstick tests were classified as no proteinuria, and this may have resulted in modest misclassification. Only health plan members who had inpatient serum creatinine measured were included. Given that serum creatinine is routinely measured among patients who are hospitalized, it is likely that patients not included would be much healthier (*e.g.*, uncomplicated pregnancies and low–risk elective procedures). These patients would be expected to be at very low risk for AKI anyway and thus, not a relevant patient population for our research question.

Patient selection after the adoption of these inclusion and exclusion criteria (Figure 1) may explain the relatively high cumulative risk of elevated BP observed in our sample. Hypertension prevalence in the United States was approximately 29%,[37] and 2-year incidence of diagnosed hypertension in two large Canadian provinces was approximately 6%–8% on the basis of age-specific estimates[38]; however, we are not aware of any recently published similar postdischarge populations to which we could compare our results.

Our primary analysis required only one BP reading to be >140/90 mmHg, because we were concerned that, in a dataset on the basis of information collected as part of routine clinical care, requiring multiple BP readings will increase bias from missing data. In addition, clinicians may treat one observed elevated BP, and therefore, requiring multiple readings may result in misclassification. In our sensitivity analysis, even stronger associations were seen between AKI status and risk of BP elevation when we required two readings of >140/90 mmHg for outcome definition.

In sum, we found that an episode of AKI during hospitalization was independently associated with an increased risk of developing elevated BP starting within the first 180 days postdischarge and that the risk was higher with greater severity of AKI. Our novel study provides the first result in adults of a connection between AKI and BP elevation, which could have important clinical and public health implications.

CONCISE METHODS

Source Population and Analysis Sample

Our cohort study population consisted of members of Kaiser Permanente Northern California (KPNC) who were ages ≥18 years old and hospitalized at least one time between January 1, 2008 and December 31, 2011. KPNC is a large integrated health care delivery system caring for >3.5 million members throughout the San Francisco and greater Bay area. Its membership is highly representative of the local surrounding and statewide population, with the exception of slightly lower representations at the extremes of age and income.[39] Nearly all of the care provided is captured through KPNC's comprehensive electronic health records, including all BP measurements obtained at ambulatory clinics of all specialties. All clinics used automated sphygmomanometers operated by trained medical assistants, with repeat measurements performed as needed by physicians using aneroid sphygmomanometers.[40]

We *a priori* selected our study population on the basis of several design considerations to minimize potential bias and confounding. Only health plan members with at least 12 months of continuous KPNC membership with drug benefits before study entry were included (Figure 1). All patients had to have prior BP measurements within 7–365 days before their index hospitalization, which was the first hospitalization during the study period. We excluded patients who were documented to have ambulatory systolic BP>140 mmHg and/or diastolic BP>90 mmHg measured between 7 and 365 days before admission as well as patients who were diagnosed to have hypertension by outpatient diagnostic codes during the 4 years before admission (codes available on request).

Because our main outcome was postdischarge BP levels, we also excluded patients who did not have at least one outpatient BP measured within 2 years of their discharge date. We also excluded patients who initiated antihypertensive agents within 7 days postdischarge before having an outpatient BP measured (to reduce the likelihood of misclassifying assignment of the postdischarge BP level).

Because chronically reduced GFR is a cause of secondary hypertension[2] as well as a risk factor for AKI,[41] we limited our study to persons who had at least one ambulatory, nonemergency room serum creatinine measured between 7 and 365 days before hospitalization. Patients on dialysis or who have undergone organ transplantation were excluded. Baseline eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[42] on the basis of the most recent eligible serum creatinine concentration found in health plan databases during the 7–365 days before admission.[20,43,44] Dipstick proteinuria was classified as being present if there was a documentation of 1+ or greater on a urine dipstick (without concurrent positive

nitrites or leukocyte esterase) up to 4 years before admission found in health plan laboratory databases.[45]

Because high body mass index is known to be risk factor for BP elevations,[46] we only included patients with known height and weight within 2 years before hospitalization on the basis of ambulatory clinic visit measurements.

Exposure

Our primary exposure was the occurrence of AKI during the index hospitalization. We defined AKI when the peak inpatient serum creatinine was higher than the baseline serum creatinine by ≥0.3 mg/dl and/or ≥50%.[47] Baseline serum creatinine is the same one used to estimate baseline GFR: the most recent ambulatory, nonemergency room serum creatinine measured between 7 and 365 days before hospitalization. We further classified the severity of AKI patterned after the KDIGO stages,[47] with dialysis-treated AKI categorized as stage 3, regardless of the magnitude of serum creatinine concentration change. Urine output was not used to define or stage AKI.

Follow-Up and Outcomes

All patients were followed for up to 2 years after their discharge date. The primary outcome was documented systolic BP>140 mmHg and/or diastolic BP>90 mmHg measured during a postdischarge ambulatory, nonemergency department visit. Patients were censored because of end of follow-up, health plan disenrollment, or death (identified from comprehensive health plan administrative databases, proxy reporting, Social Security Administration vital status files, and California state death certificate files).

Covariates

Diabetes mellitus status was defined on the basis of inpatient and ambulatory diagnostic codes, abnormal glycosylated hemoglobin level, or receipt of antidiabetic agents as part of a regional diabetes registry[48]; smoking status was defined as current or former smoker versus never smoker in ambulatory clinic databases. Prior chronic heart failure was defined as prior hospitalization with a primary discharge of heart failure or three or more ambulatory, nonemergency diagnoses of heart failure.[49] Prior coronary heart disease was defined as prior hospitalized acute coronary syndrome or receipt of coronary artery bypass surgery or percutaneous coronary intervention.[50] Targeted medication use before admission was ascertained on the basis of dispensing information from ambulatory prescriptions found in health plan pharmacy databases using previously described and validated algorithms and methods.[51–54]

Statistical Analyses

We used multivariable logistic regression to examine the association of AKI and postdischarge elevated BP. We chose not to conduct a time to event analysis, because time to ascertainment of BP is dependent on the timing of a visit to a health care provider that included a BP measurement. Instead, we examined discrete periods of time after discharge. Our primary analysis is on the basis of cumulative risk over 2 years after discharge. Because the effect of renal parenchymal injury may be more pronounced in the short term,[55] we *a priori* decided to analyze incidence by increasing lengths of time after discharge: within 180, 365, 540, and 730 days.

We also performed five separate sensitivity analyses to examine the consistency and robustness of our results.

(*1*) We excluded patients who were receiving diuretics, β-blockers, calcium channel blockers, angiotensin–converting enzyme inhibitors, and angiotensin receptor blockers at the time of hospitalization. Within the KPNC population, these four classes of drugs accounted for 81.4% of all antihypertensive medications. We did not initially exclude patients who were on these medications, because they could be prescribed for other purposes (*e.g.*, tremors, Raynaud's disease, or systolic heart failure).

(*2*) We excluded patients who had eGFR<60 ml/min per 1.73 m^2 or documented prior proteinuria, because CKD is a risk factor for hypertension.[56]

(*3*) We required at least two postdischarge readings (at separate visits) of systolic BP>140 mmHg and/or diastolic BP>90 mmHg to qualify as developing elevated BP.

(*4*) We reclassified those patients who were originally included as patients with AKI solely because of meeting a 0.3-mg/dl or greater rise in serum creatinine but who did not otherwise meet the ≥50% criterion as no AKI.[47]

(*5*) We excluded all BP readings obtained within the first 90 days of hospital discharge to ensure that any association between AKI and subsequent elevated BP was not a transient effect.

The study was approved by Kaiser Foundation Research Institute's Institutional Review Board and the University of California, San Francisco Committee for Human Research. A waiver of informed consent was obtained because of the nature of the study.

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DISCLOSURES

None.

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