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Spectrum of acute renal failure in the intensive care unit: The PICARD experience

RAVINDRA L. MEHTA, MARIA T. PASCUAL, SHARON SOROKO, BRANDON R. SAVAGE, JONATHAN HIMMELFARB, T. ALP IKIZLER, EMIL P. PAGANINI, and GLENN M. CHERTOW, FOR THE PROGRAM TO IMPROVE CARE IN ACUTE RENAL DISEASE (PICARD)

Division of Nephrology, Department of Medicine, University of California San Diego, San Diego, California; Division of Nephrology, Department of Medicine, Maine Medical Center, Portland, Maine; Division of Nephrology, Department of Medicine, Vanderbilt University, Nashville, Tennessee; Section of Extracorporeal Therapy, Department of Nephrology and Hypertension, Cleveland Clinic Foundation, Cleveland, Ohio; and Division of Nephrology, Department of Medicine, University of California San Francisco, San Francisco, California

Spectrum of acute renal failure in the intensive care unit: The PICARD experience.

Background. Acute renal failure (ARF) in the critically ill is associated with extremely high mortality rates. Understanding the changing spectrum of ARF will be necessary to facilitate quality improvement efforts and to design successful interventional trials.

Methods. We conducted an observational cohort study of 618 patients with ARF in intensive care units at five academic medical centers in the United States. Participants were required to sign (or have a proxy sign) informed consent for data collection. A comprehensive data collection instrument captured more than 800 variables, most on a daily basis, throughout the course of ARF. Patient characteristics, dialysis status, and major outcomes were determined and stratified by clinical site.

Results. The mean age was 59.5 years, 41% were women, and 20% were of minority race or ethnicity. There was extensive comorbidity; 30% had chronic kidney disease, 37% had coronary artery disease, 29% had diabetes mellitus, and 21% had chronic liver disease. Acute renal failure was accompanied by extrarenal organ system failure in most patients, even those who did not require dialysis. Three hundred and ninety-eight (64%) patients required dialysis. The in-hospital mortality rate was 37%, and the rate of mortality or nonrecovery of renal function was 50%. The median hospital length of stay was 25 days (26 days, excluding patients who died).

Conclusion. There is a changing spectrum of ARF in the critically ill, characterized by a large burden of comorbid disease and extensive extrarenal complications, obligating the need for dialysis in the majority of patients. There is wide variation across institutions in patient characteristics and practice patterns. These differences highlight the need for additional multicenter observational and interventional studies in ARF.

Acute renal failure (ARF) in the critically ill has been the topic of numerous reports over the past four decades. Many of these reports have focused on the associated high mortality rates; observational data from a broad range of centers have suggested in-hospital mortality rates in excess of 50% in most reported series [1–10]. Identification of risk factors, comparison of severity scores, and comparisons of nonrandomized treatment strategies (e.g., diuretic agents, dopamine, dialysis modality) have dominated this literature [11–21].

Arguably most striking has been the lack of obvious improvement in acute renal failure–associated mortality rates over time. Such a dilemma would typically stimulate clinical investigation, given vast potential for improvement. However, owing in part to wide variation in patient characteristics, practice patterns, and outcomes across centers and among published reports, even identifying major areas for potential intervention has been difficult. While several randomized clinical trials have been conducted in the more recent past [22–25], most have shown no benefit.

In an effort to develop a large registry of critically ill patients with ARF across multiple clinical sites, we created the Program to Improve Care in Acute Renal Disease (PICARD). The major goal of PICARD was to leverage the diversity of several sites and a relatively large sample of patients to better understand those demographic, process, renal, and nonrenal clinical factors associated with favorable and unfavorable outcomes, including mortality, nonrecovery of renal function, and resource utilization. In doing so, our hope was to provide a

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Key words: acute renal failure, cohort study, mortality, intensive care unit, severity of illness.

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Table 1. Baseline characteristics of PICARD cohort on day of nephrology consultation

Variable	*N*	All	CCF *N* = 170	MMC *N* = 93	VU *N* = 103	UCSD *N* = 89	UCSF *N* = 163	*P* value
Mean age *year*	615	59.5	63.2	69.0	56.8	52.8	55.5	<.0001
% Male	618	59%	65%	70%	58%	49%	52%	0.006
Race/ethnicity								<.0001
% Caucasian	493	79.9%	86%	99%	94%	53%	69%	
% African American	51	8.3%	11%	1%	6%	8%	12%	
% Hispanic	39	6.3%	1%	0%	0%	27%	8%	
% Asian/Pacific Islander	25	4.1%	0%	0%	0%	11%	9%	
% Other/mixed race	9	1.5%	2%	0%	0%	1%	2%	
% CKD	579	30%	44%	30%	30%	19%	19%	<.0001
% Surg pre/at ICU admission	610	38%	44%	51%	36%	29%	29%	0.002
% HTN	618	53%	65%	69%	42%	42%	43%	<.0001
% DM	618	29%	32%	41%	25%	20%	26%	0.02
% COPD	618	16%	22%	17%	20%	6%	12%	0.003
% CHF	618	28%	52%	16%	24%	9%	21%	<.0001
% CAD	618	37%	53%	51%	35%	11%	27%	<.0001
% Leukemia	599	3%	3%	1%	1%	2%	6%	0.09
% Lymphoma	618	4%	4%	2%	6%	0%	7%	0.06
% Liver disease	618	21%	9%	5%	20%	40%	31%	<.0001
% HIV positive	618	1%	0%	0%	1%	2%	1%	0.31
% Immunocopromised	618	12%	9%	5%	16%	4%	20%	0.0003
% Chemotherapy	618	9%	7%	6%	5%	3%	18%	0.0001
% Radiation therapy	618	6%	5%	6%	2%	4%	9%	0.23
% Steroid therapy	618	15%	11%	5%	17%	20%	21%	0.002
Mean Apache 3 score	536	86	79	82	87	96	90	<.0001
Mean Apache 2 score	532	20	18	19	19	22	22	<.0001
Mean # organ systems failed	550	2.9	2.3	3.3	2.8	2.9	3.2	<.0001
% CNS failure	551	20%	10%	33%	18%	40%	13%	<.0001
% Renal failure	553	95%	91%	98%	92%	99%	97%	0.02
% Liver failure	550	31%	17%	20%	26%	43%	50%	<.0001
% Hermatologic failure	553	25%	8%	20%	19%	10%	61%	<. 0001
% Cardiovascular failure	553	48%	55%	81%	54%	19%	34%	<.0001
% Respiratory failure	552	67%	53%	74%	71%	78%	69%	0.0003
Mean heart rate *per min*	594	95	90	90	102	98	97	<.0001
Mean systolic BP *mm hg*	596	115	114	118	113	115	116	0.56
Mean diastolic BP *mm Hg*	595	56	55	53	57	57	58	0.1
Mean mean arterial BP *mm Hg*	595	76	75	74	75	77	77	0.58
Mean pulse pressure *mm Hg*	595	59	58	65	56	58	59	0.02
Mean temp (deg °C)	593	37	36.8	37.0	36.9	37.0	37.2	0.06
Median UO *ml*	597	946	1264	1045	656	652	1010	0.006
% Oliguria ≤400 mL/day	597	29%	22%	14%	37%	42%	32%	<.0001
Mean resporatory rate	597	20.1	18.8	17.0	22.1	20.9	21.4	<.0001
Mean AM weight *kg*	413	87.1	84.5	88.9	89.3	82.9	89.0	0.27
Median total bilirubin *mg/dL*	339	1.7	1.1	1.1	2.1	4.2	2.6	<.0001
Mean creatinine *mg/dL*	596	3.39	3.58	3.27	3.27	3.41	3.31	0.55
Mean BUN *mg/dL*	591	65	71	59	60	73	61	0.003
Mean platelets *1000/mm^3*	545	155	157	165	172	137	148	0.26
Mean pH	342	7.35	7.37	7.34	7.3	7.36	7.35	0.005
Mean potassium *mEg/L*	593	4.6	4.6	4.6	4.6	4.7	4.6	0.96
Mean bicarbonate *mEg/L*	589	21.4	21.7	22.9	22.6	20.7	19.7	<.0001
Mean leukocyte *1000/mm^3*	558	14.0	13.1	14.4	14.6	15.1	13.9	0.59
Mean hemoglobin *g/dL*	557	10.2	10.2	10.1	10.3	10.5	10.2	0.79

contemporary view of the disease process, and to identify those areas most suitable for intervention.

In this manuscript, we describe the methods of patient selection and data acquisition, and the spectrum of collected clinical and process variables. We also report on major study outcomes, focusing on differences by clinical site, dialysis requirement, and etiology of acute renal failure. We hypothesized that there would be significant differences in patient characteristics, processes of care, and outcomes across clinical sites.

METHODS

Study participants

The PICARD network is comprised of five academic medical centers in the United States [University of California San Diego (UCSD) (Coordinating Center), Cleveland Clinic Foundation (CCF), Maine Medical Center (MMC), Vanderbilt University (VU), and University of California San Francisco (UCSF)]. Over a 31-month period (February 1999 to August 2001), all patients consulted for ARF in the intensive care unit (ICU) were

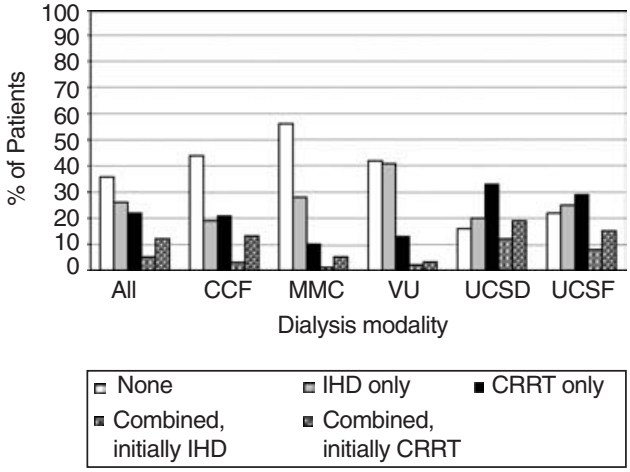

Fig. 1. The distribution of patients by dialysis status—no dialysis, IHD only, CRRT only, IHD followed by CRRT, and CRRT followed by IHD. Dialysis status × site, $P < 0.0001$. IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy.

evaluated by PICARD study personnel for potential study participation. Given the large number of ICU beds at CCF, one in six ARF patients were randomized for possible study inclusion, to avoid single center overrepresentation. Acute renal failure was defined as an increase in serum creatinine ≥0.5 mg/dL with baseline serum creatinine <1.5 mg/dL (new onset ARF), or an increase in serum creatinine ≥1.0 mg/dL with baseline serum creatinine ≥1.5 mg/dL and <5.0 mg/dL [ARF on chronic kidney disease (CKD)]. Patients with a baseline serum creatinine ≥5.0 mg/dL were not considered for study inclusion. Other exclusion criteria included age <18 years, previous dialysis, kidney transplantation, ARF from urinary tract obstruction and hypovolemia responsive to fluids; prisoners and pregnant patients were also excluded. Patients who were contacted by study personnel and who signed (or whose proxy signed) informed consents were enrolled in the study cohort. The reason for nonenrollment was determined for patients who did not sign informed consent [26], although no additional data were collected for privacy considerations. The Committees on Human Research at each participating clinical site approved the study protocol and informed consent.

Data collection strategy

If the PICARD inclusion and exclusion criteria were met and informed consent obtained, the ICU chart was reviewed to determine on which hospital day the patient met ARF criteria. Data from the first ICU day, the first day on which ARF criteria were met, the day of consultation, and the three days preceding consultation were obtained (in some instances, these days overlapped, but were appropriately coded in the database to facilitate subsequent analyses). Following consultation, data were collected prospectively until three days after the end of consultation or ICU discharge, whichever came first. For patients with extended ICU stays or prolonged dialysis requirements, data were collected for up to 10 weeks after the day of consultation, or eight weeks after the start of dialysis. Finally, data on vital status, recovery of renal function, and ICU and hospital lengths of stay were collected on the day of hospital discharge.

Data management strategy

A scannable form was developed for data capture and entry using the Teleform Designer Module (Cardiff Software, San Diego, CA, USA). The Teleform Designer generated a unique internal form ID to identify individual forms. Each PICARD site was equipped with hardware and software to print forms locally with unique patient identifiers. Study coordinators completed the forms, which were then scanned and recognized by the Teleform Reader Module. Following editing and validation of data by the Teleform Verifier Module, the data were transferred directly into the Teleform database at each site. Site computers were connected to the UCSD Data Coordinating Center server via a virtual private network on the Internet. Data from the Teleform database were encrypted and transferred via the Internet to the SQL server using a Microsoft Peer to Peer Transfer protocol (MS PPTP; Microsoft, Redmond, WA, USA) for secure connections. The data were deidentified and subjected to a variety of rules and checks to identify any errors before ultimately being transferred to the PICARD database created in Microsoft SQL 7.0 using the Microsoft Data Engine (Microsoft). Data were backed up each night, and periodic audits were performed to establish the accuracy of data capture and transfer into the database.

Data elements

Multiple data elements (>800 per patient) were collected on each PICARD participant. Data elements included: demographics, comorbid conditions, hospital and ICU admission and discharge data, ICD-9 admission and discharge diagnosis codes, presumed etiologies of ARF, vital signs, urine output, volume status (including intake and output), surgical procedures, nonsurgical procedures (e.g., radiology, echocardiography, endoscopy), blood and urine laboratory studies including microbiology, medication use, and the use of parenteral and enteral nutrition. Multiple generic and ARF-specific severity scores were calculated based on the data obtained above. Organ failure was defined using validated published criteria [18]. Dialysis procedures were evaluated in exquisite detail, including data on vascular access, anticoagulation, blood and dialysate flow rates, hemofiltration solution and dialysate composition, ultrafiltration

Table 2. Baseline characteristics by dialysis status (all sites)

Variable	Not dialyzed	IHD only	CRRT only	Initial IHD then crossover to CRRT	Initial CRRT then crossover to IHD	*P* value
Mean age (*years*)	62.9	61.7	53.6	56.3	56.2	<.0001
%Male	61%	57%	58%	47%	64%	0.51
Race/ethnicity						0.03
Caucasian	37%	26%	22%	4%	11%	
African American	47%	25%	16%	4%	8%	
Hispanic	18%	23%	28%	15%	15%	
Asian/Pacific Islander	16%	32%	28%	8%	16%	
Other/mixed race	33%	33%	11%	11%	11%	
% CKD	34%	38%	17%	34%	22%	0.001
% Surg pre/at ICU admission	43%	36%	31%	32%	39%	0.22
% HTN	60%	54%	41%	53%	46%	0.007
% DM	33%	29%	23%	28%	28%	0.44
% COPD	17%	17%	11%	25%	17%	0.35
% CHF	32%	24%	28%	31%	22%	0.36
% CAD	49%	36%	24%	28%	28%	<.0001
% Leukemia	3%	1%	6%	0%	4%	0.08
% Lymphoma	3%	3%	8%	0%	7%	0.05
% Liver disease	14%	21%	28%	31%	22%	0.008
% HIV positive	1%	1%	0%	0%	1%	0.72
% Immunocompromised	10%	11%	15%	13%	13%	0.66
% Chemotherapy	8%	8%	13%	3%	10%	0.24
% Radiation therapy	5%	5%	7%	6%	4%	0.87
% Steroid therapy	11%	14%	19%	31%	14%	0.02
Mean Apache 3 score	77	84	99	82	92	<.0001
Mean Apache 2 score	16	17	21	20	21	<.0001
Mean # organ systems failed	2.6	2.7	3.5	3.2	2.9	<.0001
% CNS failure	15%	16%	33%	23%	97	0.001
% Renal failure	92%	97%	95%	95%	97%	0.30
% Liver failure	19%	29%	50%	50%	31%	<.0001
% Homatologic failure	18%	21%	41%	32%	23%	<.0001
% Cardiovascular failure	54%	44%	50%	36%	40%	0.11
% Respiratory failure	57%	60%	84%	68%	77%	<.0001
Mean heart rate *per min*	93	90	102	89	99	<.0001
Mean systolic BP *mm Hg*	116	122	105	122	113	<.0001
Mean diastolic BP *mm Hg*	56	58	51	62	57	0.0003
Mean mean arterial BP *mm Hg*	76	79	69	82	76	<.0001
Mean pulse pressure *mm Hg*	60	64	54	60	55	.0003
Mean temp °C	37.0	36.8	37.1	36.9	36.9	0.32
Median UO *mL/day*	1643	465	669	967	467	<.0001
% Oliguria ≤400 mL	10%	42%	34%	34%	46%	<.0001
Mean respiratory rate *per min*	19	20	21	20	21	0.09
Mean AM. weight *kg*	86	85	91	85	91	0.18
Median total bilirubin *mg/dL*	1.2	1.3	3.3	1.7	1.5	<.0001
Mean creatinine *mg/dL*	3.0	3.9	3.3	3.5	3.7	<.0001
Mean BUN *mg/dL*	59	69	68	75	65	0.03
Mean platelets *1000/mm^3*	162	163	126	159	170	0.02
Mean pH	7.37	7.33	7.36	7.33	7.34	0.08
Mean potassium *mEq/L*	4.47	4.77	4.60	4.70	4.68	0.03
Mean bicarbonate *mEq/L*	22.9	20.8	20.5	19.7	20.3	<.0001
Mean Leukocyte *1000/mm^3*	13.9	14.2	14.1	13.5	14.4	0.99
Mean hemoglobin *g/dL*	10.0	10.5	10.2	10.5	9.9	0.18

prescription and weight loss achieved, along with dialysis-associated medications, transfusions, and complications.

Outcomes

In-hospital mortality was the primary outcome; we also collected ICU mortality and 28-day mortality. Recovery of renal function was defined as dialysis independence for at least three days prior to discharge. We considered the combined outcome of death or nonrecovery (dialysis dependence) after ARF. Finally, we collected information on hospital and ICU lengths of stay.

Dialysis and nondialysis care

Intermittent dialysis was performed using volumetrically controlled, bicarbonate-based machines and synthetic biocompatible hemodialyzers. The indications, frequency, and duration of intermittent dialysis treatment were individualized for each patient based on prevalent practices at each clinical site. Continuous techniques included continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), and continuous veno-venous hemodiafiltration (CVVHDF). Operational characteristics for each modality were

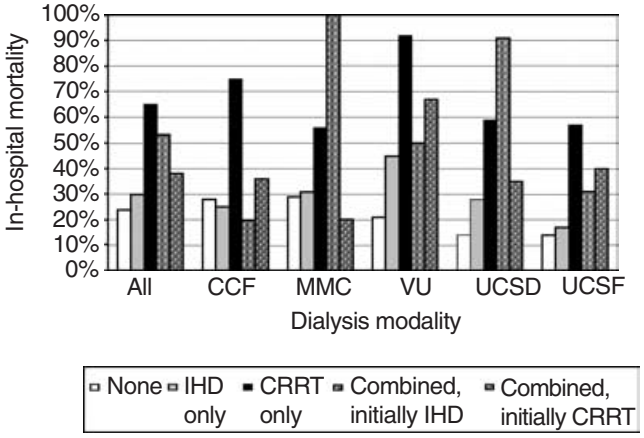

Fig. 2. In-hospital mortality by dialysis status. Mortality × dialysis status, $P < 0.0001$; mortality × dialysis status × site, $P < 0.0001$.

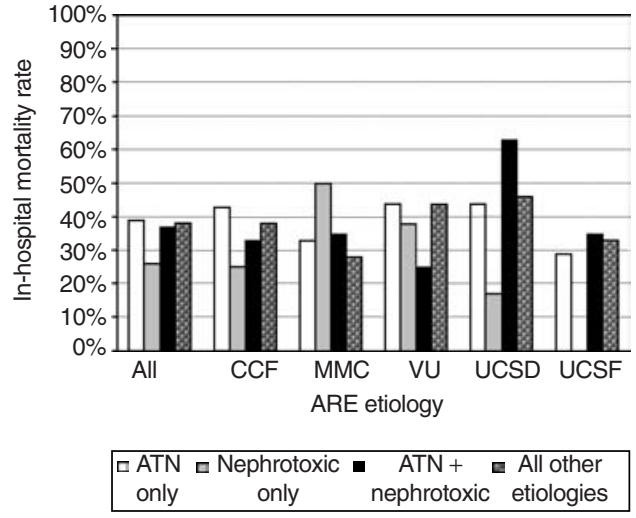

Fig. 3. In-hospital mortality by presumed acute renal failure (ARF) etiology—ischemic acute tubular nephropathy (ATN), nephrotoxic ARF, both, or other. Mortality by etiology, $P = 0.71$; mortality × etiology × site, $P = 0.81$.

determined by the treating nephrologists at each clinical site. There were no prespecified criteria for initiation or withdrawal of dialysis or for any aspect of dialysis care. Concurrent ICU care for each patient was determined by the treating physicians in conjuction with nephrologists. No interventions were instituted as part of the PICARD study.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median and interquartile range and compared using analysis of variance (general linear models with adjustment for multiple comparisons) or the Kruskal-Wallis test where appropriate. Categorical variables are expressed as proportions and compared with the Cochran-Mantel-Haenszel χ^2 test or Fisher exact test. Two-tailed P values < 0.05 were considered significant. Statistical analyses were conducted using SAS 8.2 (SAS Insitute, Cary, NC, USA).

RESULTS

Baseline characteristics

There were 618 patients enrolled in PICARD. Demographic data were obtained on virtually all patients, as were data on comorbid conditions and the presumed etiology of ARF. Vital signs, urine output, and routine laboratory studies were obtained on more than 95% of patients. Data sufficient to calculate the Acute Physiology and Chronic Health Evaluation (APACHE) III and other severity of illness scores were available in 94% of patients. Other laboratory studies, procedures, and other data elements were similarly well captured, although less widely available due to the nonroutine nature of the information. As hypothesized, there were significant differences in numerous baseline characteristics, processes of care, and outcomes by site.

Table 1 shows an array of baseline data from the day of consultation, stratified by clinical site. The mean age was 59.5 years, though varied widely across sites. The majority of patients were white, with a modest fraction of African American patients at four of five sites. There was a modest fraction of Hispanic and Asian/Pacific Islander patients, although these were derived exclusively from the two California sites. Comorbid conditions were common, although specific comorbidities varied widely by site. Patients at CCF and MMC had more extensive cardiovascular comorbidities (hypertension, coronary artery disease, and heart failure) owing in part to the older ARF populations served. In contrast, liver disease and immunosuppression were more common among patients at UCSD and UCSF. Respiratory failure was common among ARF patients at all sites. The distribution of other failed organ systems differed significantly. There were surprisingly few intersite differences in vital signs or body weight. The median urine outputs were lowest and the fraction of patients with oliguria highest at VU and UCSD. Mean leukocyte counts were elevated, and hemoglobin concentrations were reduced, consistent with a high incidence of infection and inflammation. The pH and bicarbonate concentrations were low, consistent with metabolic acidosis. Aside from the total bilirubin concentration (corresponding to the fraction of patients with acute and chronic liver disease), there were relatively few differences across sites in baseline laboratory data. Likewise, the distribution of presumed etiologies of ARF was relatively uniform, except for a lower fraction of patients with "prerenal" azotemia at MMC, and a higher fraction of patients with ARF associated with liver disease at UCSF.

Table 3. Several recent studies of ARF in the ICU

Variable	Ref.	Year	*N*	Location	% Mortality No dialysis	Dialysis
Brivet et al	[3]	1996	360	Multicenter, France	43%	64%
Liano et al	[6]	1998	748	Multicenter, Spain	53%	79%
De Mendonca et al	[32]	2000	1411	16 countries, Eurpoe	NA	44%
Silvester et al	[7]	2001	299	Multicenter, Australia	NA	47%
Metniz et al	[33]	2002	839	Multicenter, Austria	39%	63%
Clermont et al	[8]	2002	254	Pittsburgh, USA	23%	57%
Guerin et al	[28]	2002	587	Multicenter, France	NA	71%
Metcalfe et al	[9]	2002	89	Multicenter, Scotland	NA	74%
Mehta et al	[18]	2002	605	Multicenter, California, USA	39%	61%
PICARD		2003	618	Multicenter, USA	24%	45%

Dialysis status

Three hundred and ninety-eight (64%) patients were dialyzed for ARF. The overall utilization of continuous renal replacement therapy (CRRT) was high, with 60% of dialyzed patients receiving CRRT for all or part of their dialysis course. Figure 1 shows the distribution of patients by dialysis modality [none, intermittent hemodialysis (IHD) only, CRRT only, IHD followed by CRRT, and CRRT followed by IHD] and stratified by site. Patients at MMC (63%) and VU (70%) were more likely to undergo IHD alone than patients at the other three sites (24% to 34%).

Table 2 shows the frequency of baseline characteristics by dialysis status. Patients who did not require dialysis were more likely to have been hypertensive with a history of coronary artery disease. Higher urine output and lower APACHE III scores were also associated with nondialysis-requiring ARF. The heart rates were higher, and systolic, diastolic, and mean arterial blood pressures lower among patients treated with CRRT. Continuous therapy use was also associated with acute hepatic failure and the total bilirubin concentration.

Mortality, mortality or nonrecovery, and lengths of stay

The overall in-hospital mortality rate was 37% (231/618). The 28-day mortality rate was 22% (138/617; the admission date was missing for one patient), and the ICU mortality rate was 32% (199/618). Figure 2 shows overall and site-specific in-hospital mortality by dialysis status—no dialysis, IHD only, CRRT only, and combined IHD + CRRT by initial dialysis modality. As expected, in-hospital mortality rates were higher among patients who required dialysis, particularly those selected for CRRT. Patients with ARF superimposed on CKD had lower mortality rates than those with new-onset ARF (31% vs. 41%, $P = 0.03$). Figure 3 shows overall and site-specific in-hospital mortality rates by the presumed etiology of ARF. For these analyses, mutually exclusive categories were created—ischemic ATN, nephrotoxic ARF, both, and other. There was no relation between presumed etiology of ARF and in-hospital mortality. An expanded description of the presumed etiology of ARF (allowing more than one etiology per case) is shown in Table 4. Figures 4 and 5 show the combined outcome of mortality or nonrecovery by dialysis status and ARF etiology, respectively. When considering the combined outcome of mortality or nonrecovery compared with mortality alone, the differences among dialysis modalities were attenuated.

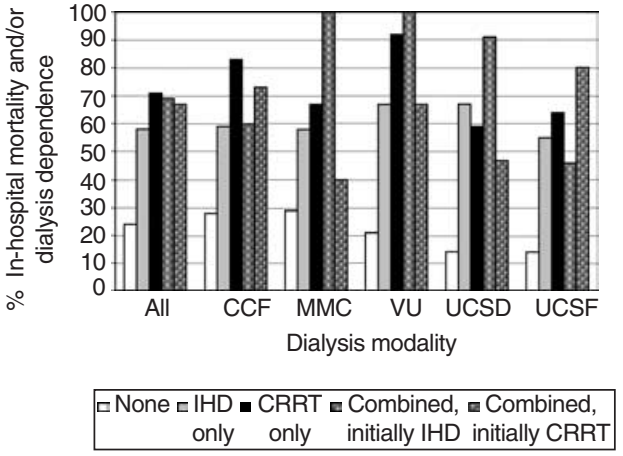

Fig. 4. Mortality or nonrecovery by dialysis status. Combination outcome by dialysis status, $P < 0.0001$; combination outcome by dialysis status × site, $P < 0.0001$.

Mortality rates were related to the severity of extrarenal disease. Figure 6 shows overall and site-specific in-hospital mortality rates by the number of failed organ systems (an additive sum of cardiovascular, hepatic, hematologic, neurologic, renal, and respiratory failure). Mortality rates exceeded 50% with four or more failed organ systems. The median hospital length of stay was 25 days (26 days when excluding patients who died).

DISCUSSION

The PICARD cohort may be the most comprehensive registry of critically ill patients with ARF assembled to date. Nonetheless, the study could not have been conceived or implemented without the prior work conducted by many committed investigators over the past

Table 4. Presumes etiologies of ARF

Presumed etiologies	*N*	% of Total
Ischemic (non-nephrotoxic) ATN		
Acute tubular necrosis precipitant not necessarily specified	311	50%
Sepsis	119	19%
Hypotension	123	20%
Renal artery thrombosis, stenosis, or trauma	6	1%
Aortic dissection or aneurysm repair	6	1%
Prolonged surgical clamping	5	1%
Vascular, unspedcified	8	1%
Cortical necrosis	2	<1%
Nephrotoxic ARF, associated with		
Calcineurin inhibitors	19	3%
Over-the-counter medications	4	1%
Other prescription medications	8	1%
Chemotherapy	7	1%
Illicit drugs	1	<1%
Aminoglycosides	8	1%
Antibiotics	19	3%
Nonsteroidal antiinflammatory drugs	2	<1%
Radiocontrast	54	9%
Rhabdomyolysis	24	4%
Tumor lysis syndrome	5	1%
Combined nephrotoxic	8	1%
ARF with inflammatory, infectious, or malignant disease		
Disseminated intravascular coagulation	6	1%
Malignant hypertension	2	<1%
Glomerulonephritis	11	2%
Interstitial nephritis	6	1%
Pyelonephritis	1	<1%
Bacterial endocarditis	2	<1%
Atheroembolic disease	1	<1%
Multiple myeloma	3	<1%
Systemic lupus erythematosus	6	1%
Hemolytic uremic syndrome	6	1%
Thrombotic thrombocvtopenic purpura	3	<1%
Other vasculitis	1	<1%
HIV-associated nephropathy	1	<1%
Multiple myeloma	3	<1%
Other neoplasms	8	1%
Extrarenal infections	2	<1%
ARF due to cardiac disease, associated with		
Myocardial infarction	14	2%
Congestive heart failure	55	9%
Valvular heart disease	9	1%
Cardiogenic shock	37	6%
Cardiorenal syndrome	8	1%
Tamponade	4	1%
ARF due to unresolved prerenal factors, associated with		
Hemorrhage	29	5%
Hypovolemia	42	7%
Anaphylaxis	1	<1%
Autonomic nervous system failure	5	1%
Nausea and vomiting	6	1%
Diarrhea	15	2%
ARF due to liver disease, associated with		
Hepatorenal syndrome	39	6%
Cirrhosis	11	2%
Hepatitis	7	1%
Liver disease, unspecified	10	2%
ARF with urinary tract obstruction		
Nephrolithiasis	2	<1%
Tumors	1	<1%
Prostate disease	1	<1%
Urinary tract obstruction, cause unspecified	4	1%
Multifactorial		
Mixed ARF with no primary designation	40	6%

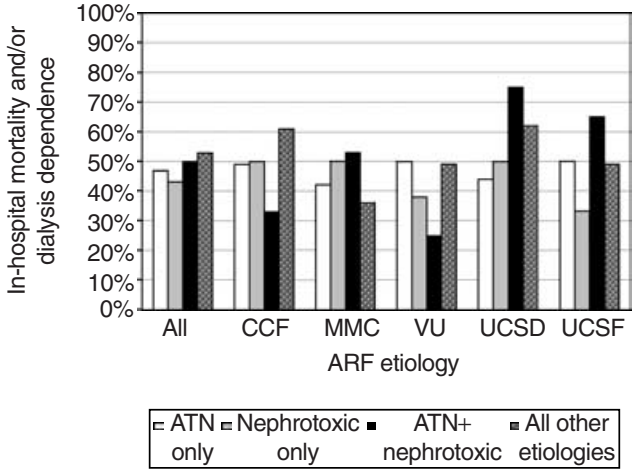

Fig. 5. Mortality or nonrecovery by presumed acute renal failure (ARF) etiology. Combination outcome by etiology, $P = 0.25$; combination outcome by etiology × site, $P = 0.65$.

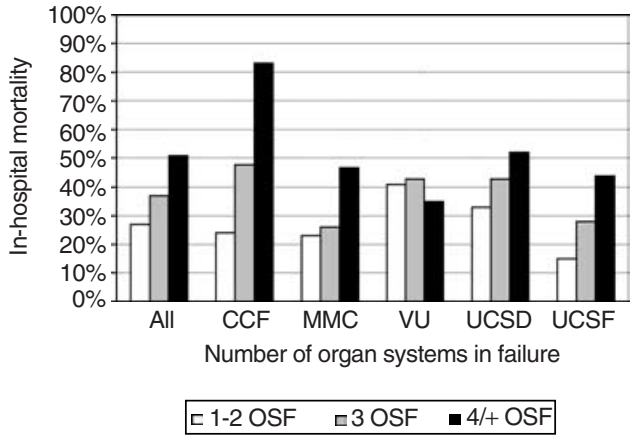

Fig. 6. In-hospital mortality by number of organ systems failed (OSF). Mortality × number OSF, $P < 0.0001$; mortality × number OSF × site, $P < 0.0001$.

40 years. Indeed, the plight of critically ill patients with ARF has been the subject of dozens of published reports, some dating back to the 1960s. A brief review of several of these reports highlights the changing spectrum of ARF over time. Kleinknecht et al [27] published a case series of 500 patients with ARF seen between 1966 and 1970. Two hundred and twenty-one patients received "prophylactic" hemodialysis to maintain the urea concentration below 200 mg/dL (corresponding to a BUN <93 mg/dL). Compared with 279 patients cared for in earlier years (during which dialysis was initiated if the urea concentration was >350 mg/dL (BUN >164 mg/dL) or because of other severe electrolyte disturbances, patients treated with prophylactic hemodialysis experienced fewer uremic complications and had a significantly lower mortality rate. McCarthy [5] reported a "tale of two eras," in which he compared an institution's experience during the

late 1970s with the same institution's experience during the early 1990s. He found higher survival rates during the latter era, despite having more complicated causes of ARF. Data from Brivet et al [3], Liano et al [4, 6], and others [15, 28–31] have also suggested that while overall mortality rates associated with ARF have not materially improved, the number and complexity of extrarenal complications in patients with ARF has indeed increased. Table 3 summarizes ARF-associated mortality rates derived from several more recently published studies.

Data from PICARD suggest that the trend toward more complicated ARF continues into the 21st century. More than half of patients with ARF in the ICU require dialysis, and a large fraction has significant hemodynamic instability. Among the 134 patients who required dialysis and were assigned to CRRT alone, the average mean arterial blood pressure was below 70 mm Hg despite the use of pressor agents. These same patients had, on average, between three and four failed organ systems. Therefore, despite crude mortality rates that have remained high, it is reasonable to conclude that outcomes associated with ARF in the critically ill have indeed improved, at least marginally, in the recent past.

There are several limitations to the information presented here. First, PICARD included academic medical centers providing extensive tertiary care. Therefore, we may have overestimated the associated comorbidity and severity of illness relative to what would be expected across institutions providing mainly primary and community-based care. Second, it is difficult to categorize the presumed etiology of ARF by clinical criteria. Given considerable overlap and potential misclassification, we may have erred in not identifying etiology-specific differences in mortality or nonrecovery. More precise determinations of the etiology of ARF, including biopsy, would be desirable in future studies. Third, because patients were identified after nephrology consultation, we did not ascertain cases that might have "qualified" by ARF diagnosis criteria but were not deemed sick enough to require consultation, or who were so sick that nephrology consultation was considered irrelevant. The requirement that participants or their proxies signed informed consent was associated with a large fraction of potential cases not being enrolled [26]. While detailed data were not available on nonenrolled patients, many were not enrolled because they expired before informed consent could be obtained. In other words, patients who were healthy enough to sign informed consent (or who had attendant family members or friends) were likely to be different than "all comers" with ARF in the ICU. Therefore, PICARD may have underestimated ARF-associated mortality rates at the participating institutions. Finally, we demonstrated wide variation across sites, and the number of sites was relatively small. Incorporating additional sites in future efforts should provide an even clearer picture of contemporary ARF in the ICU.

CONCLUSION

ARF in the critically ill remains an extremely important problem facing nephrologists and other intensivists. The proportion of patients requiring dialysis is high; institutions with continuous dialysis capability appear to be using these techniques with increasing frequency. There is a considerable burden of extrarenal disease affecting patients before or concurrent with the ARF episode. There is wide variation across institutions in patient characteristics and practice patterns. These differences highlight the need for additional multicenter observational and interventional studies in ARF.

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Reprint requests to Glenn M. Chertow, M.D., MPH, University of California San Francisco, Department of Medicine Research, UCSF Laurel Heights Suite 430, 3333 California Street, San Francisco, CA 94118–1211. E-mail: chertowg@medicine.ucsf.edu

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