Long-term outcome of acute tubular necrosis: A contribution to its natural history

F Liaño[1,2], C Felipe[1], MT Tenorio[1], M Rivera[1], V Abraira[3], JM Sáez-de-Urturi[4], J Ocaña[1], C Fuentes[5] and S Severiano[5]

[1]Nephrology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain; [2]Department of Medicine, School of Medicine, Universidad de Alcalá, Alcalá de Henares, Spain; [3]Department of Clinical Biostatistics, Hospital Universitario Ramón y Cajal, Madrid, Spain; [4]Clinical Documentation and Archives Department, Hospital Universitario Ramón y Cajal, Madrid, Spain and [5]Department of Health Information of the Community of Madrid, Madrid, Spain

As long-term outcome studies of acute renal failure (ARF) are scarce and non-homogeneous, we studied 187 consecutive acute tubular necrosis (ATN) patients without previous nephropathies, discharged alive from our hospital between October 77 and December 92 and followed-up until December 99 (range 7–22 years; median 7.2). Variables were analyzed at the time of the acute episode and during follow-up. In 2000–2001 a clinical evaluation was made in 58 of the 82 patients still alive. Ten patients were lost to follow-up and 95 died. In 59% death was related with the disease present when the ATN developed. Kaplan–Meir survival curve showed 89, 67, 50, and 40% at 1, 5, 10, and 15 years, respectively, after discharge. Survival curves were significantly better (log-rank $P<0.001$) among the youngest, those surviving a polytrauma, those without comorbidity and surprisingly those treated in intensive care units. The proportional Cox model showed that age (hazard ratio (HR) 1.04 per year of age; $P=0.000$), presence of comorbid factors (HR 4.29; $P=0.006$), surgical admission (HR 0.45; $P=0.000$), and male sex (HR 1.72; $P=0.020$) were the variables associated with long-term follow-up. In the evaluated patients renal function was normal in 81%. Long-term outcome after ARF depends on absence of co-morbid factors, cause of initial admission and age. Although the late mortality rate is high and related with the original disease, renal function is adequate in most patients.

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Correspondence: *F Liaño, Department of Nephrology, Hospital Ramón y Cajal, Carretera de Colmenar Km 9,100, 28034-Madrid. Spain. E-mail: lianof@yahoo.es*

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During the last half century, studies concerning long-term survival after an acute renal failure episode (ARF) have been few and non-homogeneous[1–10] with a follow-up period ranging between 6[5] and 372 months.[1] Only four studies include more than a hundred patients in their long-term studied population.[1,2,9,10] Additionally, with the exception of age on the functional outcome,[4,11,12] few variables that could potentially influence either the functional or long-term outcome of patients surviving an ARF episode have been studied. Consequently, the influence that an ARF episode has on long-term outcome of the surviving patients is almost unknown. However, most of the medical community consider, without any contrasted evidence, that ARF has no influence on the long-term outcome of surviving patients.

To clarify these aspects, we developed a protocol to study the factors that could affect the personal and functional long-term outcomes of patients who, having previously had a normal kidney function, developed and survived acute tubular necrosis (ATN), which is both the most usual and severe form of ARF.[5,13] In this article we analyze the long-term survival of 187 ATN patients consecutively discharged alive at Ramón y Cajal Hospital between 1977 and 1992. They all had a potential minimal observational period of 7 years.

RESULTS

Of an initial population of 413 ARF cases, the 187 surviving patients (45%) constituted the population analyzed (Table 1). Only 10 of the 187 patients were lost to follow-up (95%follow-up rate). The remaining 177 patients were followed between 6 months and 22 years. Fifty percent of the patients had a follow-up of 7.2 years (P25: 2.0 years and P75:11.6 years). The probability of these patients being alive 10 years after discharge was 50%. (Figure 1).

All the variables given in 'Materials and Methods' were analyzed using the Kaplan–Meir curves. There were no differences in the survival curves (not shown) in relation with sex, ATN etiology, individual severity index (ISI), need of dialysis, ARF functional severity, presence/absence of oliguria or the degree of renal function at discharge.

Survival rates at 10 years for patients younger than 31, between 31 and 50, 51 and 70, and older than 70 years of age

Table 1 | Characteristics of the survivor patients at the moment of the acute tubular necrosis renal failure episode

	Patients	
	(No=187)	(%)
Age/years	57.8±16.2	
Gender (female/male)	63/124	34/66
Comorbidity factors (no/yes)	35/152	19/81
Type of admission		
Medical	95	51
Surgical	81	43
Trauma	11	6
ATN etiology		
Nephrotoxic	97	52
Sepsis	26	14
Medical	32	17
Surgical	32	17
Severity Index (SI)	0.31±0.2	
ARF functional severity		
Mild	20	11
Moderate	79	42
Severe	88	47
Type of ARF		
Oliguric	72	39
Non oliguric	115	61
Dialysis		
Yes	57	30
No	130	70
ICU admission		
Yes	80	43
No	107	57
ICU stay (days)	14.7±14.0	
Recovery of renal function with respect to serum creatinine at admission		
Total recovery	78	42
Partial recovery	107	57
No recovery	2	1
Renal function at discharge		
Normal renal function	78	42
Mild renal insufficiency	64	13
Moderate renal insufficiency	39	21
Severe renal insufficiency	6	3
Dialysis	0	
Final serum creatinine (mg/dl)	1.7±0.7	
Length of admission (days)	53.9±36.9	
Length of nephrological care (days)	18.9±13.6	

ARF, acute renal failure episode; ATN, acute tubular necrosis; ICU, intensive care unit; SI, severity index.
Continuous variables are expressed as mean±s.d.

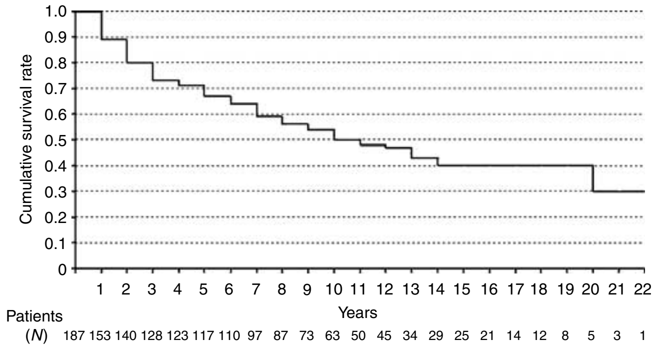

Figure 1 | Kaplan–Meier survival curve of the patients discharged alive after an ATN episode.

were 64, 78, 50, and 18%, respectively. The survival curves of these four groups of patients had statistically significant differences (log-rank $P=0.000$) (Figure 2a). There were no statistical differences between the survival curves of the group of patients younger than 31 years and that of patients with ages ranging between 31 and 50 years ($P=0.172$). The comparisons between the survival curves of the other age groups are shown in Figure 2a. A similar analysis grouping the patients by decades gave similar results. The survival curve of each decade was worse than that of the preceding one with the exception of the patients younger than 21 who had a worse survival curve than that of the patients with ages ranging between 21 and 30 years of age (not shown).

The probability of survival at 10 years after discharge for patients having a trauma, surgical or medical admission was 84, 53, and 44%, respectively. The survival curves of these three different types of admission were statistically different (log-rank $P=0.041$) (Figure 2b).

The survival curve of patients without comorbid factors was significantly better (log-rank $P=0.000$) than that of patients with associated comorbid processes (Figure 2c). At 10 years after discharge, the survival rate was 85% in the first group and 42% in the second.

When we analyzed individually the survival curves of the different comorbid pathologies considered in this study, no statistical difference was observed among them (data not shown). This could be due to the small number of patients in each subgroup. Also, the fact that 48% of the patients had at least two comorbid factors could have contributed to these figures.

During the follow-up 95 patients died. Ninety-one of them (97%) had comorbidity factors at the time of ARF. The causes of death among the four patients without comorbidity factors were an acute myocardial infarction, urinary sepsis associated with a permanent urinary catheter, drug overdose, and one unknown. At the time of death, two of these patients had normal renal function and the others had mild renal insufficiency.

The survival curve of patients treated in an intensive care unit (ICU) setting was significantly better (log-rank $P=0.002$) than that of patients treated in other hospital areas. At 10 years the survival rate was 61 and 42% for ICU and non-ICU patients, respectively (Figure 2d).

Long-term outcome, assessed by the survival curves, was better among those patients who at the time of hospital discharge had completely recovered their renal function than among those with only partial recovery (log-rank $P=0.028$)

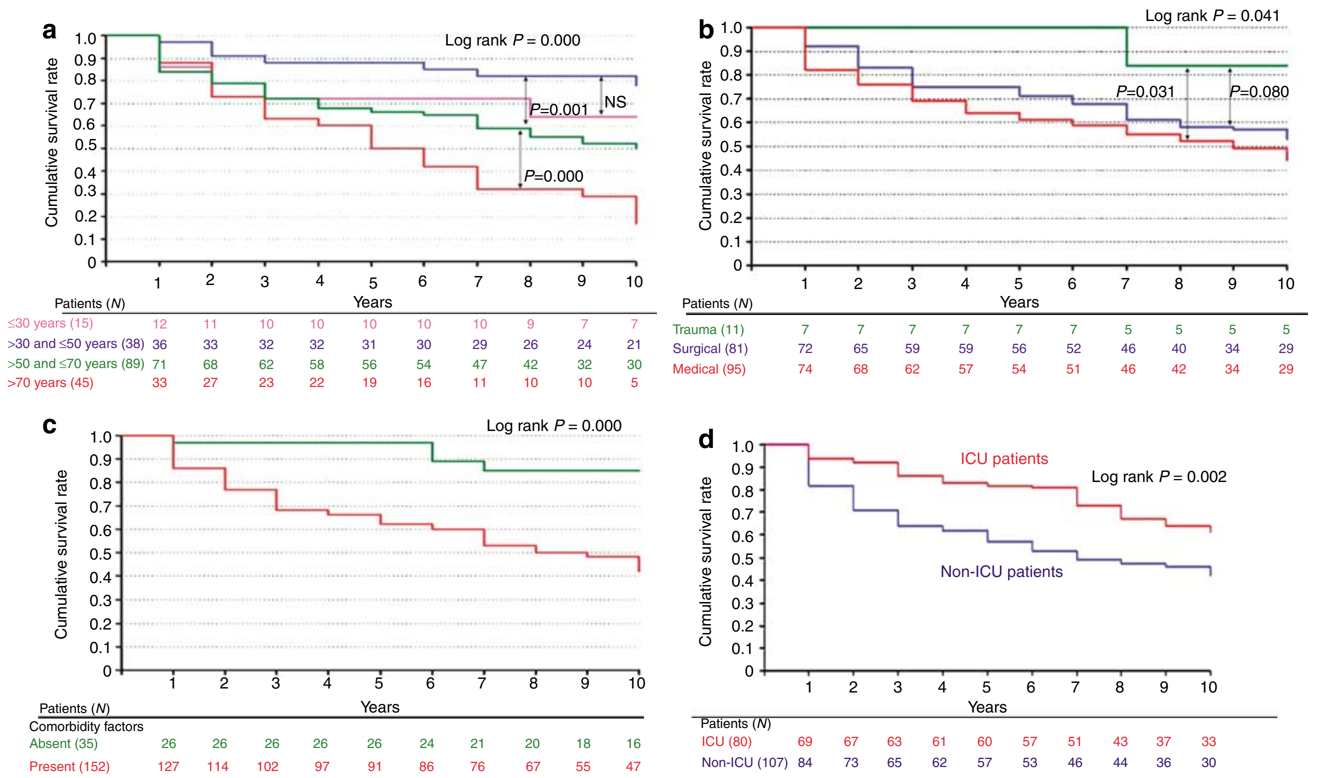

Figure 2 | Kaplan–Meier survival curves according to: (a) age; (b) the type of hospital admission; (c) the presence or absence of co-morbid conditions, and (d) the need or not of intensive care treatment during the ARF episode.

(figure not shown). The survival rates at 10 years were 60% in the first group and 43% in the second.

Cox proportional model analysis showed that the independent variables predicting the long-term outcome were: age, gender, presence of comorbidity factors and cause of initial admission (Table 2).

Indeed, according to this analysis, the risk of death increased 4% per year of age. Also, the presence of comorbidity factors when the ARF developed implied a fourfold higher relative risk of death than that observed among patients without comorbidity problems.

In general, the type of admission had important predictive significance ($P = 0.000$) on long-term survival of ATN patients. Analyzing the three admission groups, and using the risk of mortality of the medical admissions as reference value, the hazard ratios (HRs) for surgical (HR 0.45; $P = 0.000$) and trauma admissions (HR 0.42; $P = 0.397$) were lower (Table 2). There was no difference in the HR for mortality between medical and trauma groups.

Male long-term outcome was poorer than that of females (HR 1.72; $P = 0.020$).

The cause of death during the follow-up was analyzed in 86 of the 95 deaths. Mortality was attributed to one isolated cause in 80.2% of the cases. It should be stressed that the death of 59% of the patients was due to the initial disease present when the ARF episode developed.

Although a profound analysis of the long-term outcome of the kidney function is not the aim of this article, some data is given. Serum creatinine concentration (SCr) (mean ± s.d.) at hospital discharge (1.7 ± 0.7 mg/dl) decreased until the sixth month (1.3 ± 0.5 mg/dl), after which it remained reasonably stable during the 10 years of follow-up analyzed. During the follow-up three patients (1.7%), with severe comorbidity factors and age at the ATN episode ranging between 26 and 53 years, required chronic hemodialysis at 6, 11, and 12 years after discharge.

Last clinical evaluation

During 2000–2001, 58 of the 82 patients alive at the end of the study period agreed to have a complete check-up. The mean time since the ARF episode was 11.9 years. Fifty percent of the patients had a follow-up period of 10.8 years (P25: 8.5 and P50: 14.8 years). Mean age at the moment of the last clinical evaluation was 61.4 ± 14.0 years (range, 24–86 years). Males ($n = 34$) and females ($n = 24$) were similar in age.

Sixteen of the evaluated patients (28.5%) had no comorbidity factors. Although the group of patients with comorbidity factors was older (63.4 ± 13.3 years) than that of patients without comorbidity factors (56.8 ± 18.1 years), this difference was not statistically significant ($P = 0.132$). At this time, 46 patients had normal renal function (at hospital discharge functional situation was: 27 normal renal function; 13 mild renal insufficiency and six moderate or severe renal insufficiency), nine patients had mild renal failure (at hospital discharge: two had normal renal function; four mild renal insufficiency, and three moderate or severe renal

Table 2 | Should be rebuilt as follows

	Reference value	Regression coefficient	*P*	HR	CI
Age		0.04	0	1.038	1.02–1.06
Type of admission:			0		
Surgical	*Medical admission*	−0.8	0	0.45	0.29–0.70
Trauma		−0.88	0.397	0.42	0.05–3.16
Presence of Comorbidity factors	*Absence of comorbidity*	1.46	0.006	4.29	1.51–12.17
Sex	*Female*	0.54	0.02	1.72	1.09–2.72

CI, confidence interval; HR, hazard ratio.
Log likelihood ratio: X^2=52.59; *P*=0.000.

Table 3 | Analytical data of the acute tubular necrosis surviving patients in their last clinical evaluation during 2000–2001

Parameter[a]	Normal renal function (*n*=46)	Mild renal insufficiency (*n*=9)	Moderate renal insufficiency (*n*=2)
Plasma (n=57)			
Creatinine (mg/dl)	1.1 ± 0.2	1.7 ± 0.1	3.3 ± 1.5
Urea (mg/dl)°°	45.3 ± 35.0	75.1 ± 35.7	103.0 ± 21.2
Na (mEq/l)	140.0 ± 2.3	138.8 ± 6.1	142.3 ± 2.8
K (mEq/l)	4.4 ± 0.5	4.4 ± 0.3	4.6 ± 0.5
Cl (mEq/l)	105.7 ± 4.0	102.5 ± 3.7	105.5 ± 0.7
Total CO_2 (mEq/l)	28.2 ± 3.0	28.1 ± 2.0	24.6 ± 3.6
Uric acid (mg/dl)	5.9 ± 1.4	6.7 ± 2.2	9.2 ± 3.5
Glucose (mg/dl)	115.2 ± 46.3	113.4 ± 26.2	118.2 ± 33.5
Total proteins (mg/dl)	7.3 ± 0.7	7.1 ± 1.3	7.6 ± 0.3
Hemoglobin (g/dl)	15 ± 1.4	13.9 ± 3.2	11.6 ± 1.3
Hematocrit (%)	44.3 ± 4.0	41.8 ± 3.0	36.1 ± 5.8
Urine (n=40)			
Creatinine (mg/dl)	104,7 ± 49.0	71.0 ± 29.0	45.5 ± 14.8
Urea (g/l)	18.6 ± 6.0	11.2 ± 5.0	7.1 ± 2.0
Na (mEq/l)	116.0 ± 1.0	88.7 ± 4.3	76.9 ± 4.6
K (mEq/l)	39.0 ± 1.9	30.0 ± 2.2	18.0 ± 2.6
Cl (mEq/l)	100.5 ± 40.0	94.6 ± 41.0	67.8 ± 35.0
Proteinuria* (mg/min)	0,43 ± 1.18 (*n*=12)**	0.43 ± 0.45 (*n*=4)	0.54 ± 0.03 (*n*=2)
Creatinine clearance (ml/min)	101.3 ± 26.4 (*n*=29)	52.1 ± 12.1 (*n*=9)	37.3 ± 2.5 (*n*=2)

To convert urea to BUN values, in mg/dl, divide by 2.14.
[a]Values are expressed as mean ± s.d.
*Means estimate only the values of patients with positive proteinuria.
**This group includes several patients with diabetes, one of them with nephrotic proteinuria.

insufficiency), two patients had moderate renal failure (at hospital discharge one was in the same situation and the other had mild renal insufficiency) and finally one patient was in periodic hemodialysis (at hospital discharge he had moderate renal failure). With the exception of the patient on chronic hemodialysis, the analytical data of these patients are shown in Table 3.

All the inhabitants ⩾15 years of age living in Madrid on 1 January 1978 were studied as a cohort. The survival curve of this cohort is shown in Figure 3a and compared graphically with that of the patients who survived an ATN episode. It can be clearly appreciated that the slope of the curve of patients having had ARF is worse than that observed in the general population. A similar analysis, sub-classifying the patients and the general population in three subgroups of age, also demonstrated that the poorer vital expectative of patients with ARF in comparison with the general population was not conditioned by an age effect (Figure 3b).

DISCUSSION

Methodologically, as the ARF syndrome has many etiologies, we limited the study only to patients having ATN owing to the fact that: (1) ATN is the paradigmatic form of the syndrome;[14] (2) it is the most frequent type of ARF observed in developed countries,[5,15] and (3) it would allow us to manage a more homogeneous population for analysis. To avoid methodological bias, in the analysis we only included patients with a SCr < 1.4 mg/dl and ARF in organ transplant patients was excluded. The methods used were singular with respect to: (1) the period of inclusion, 15 years; (2) the prolonged period of potential follow-up of the patients, from 7 to 22 years; (3) the number of patients analyzed; (4) the small percentage of patients with unknown evolution; and (5) the fact of studying not only the survival outcome but also the renal functional outcome. In fact, on analyzing the literature (Table 4) we found that: (1) the long-term follow-up period of the patients studied is very variable, ranging

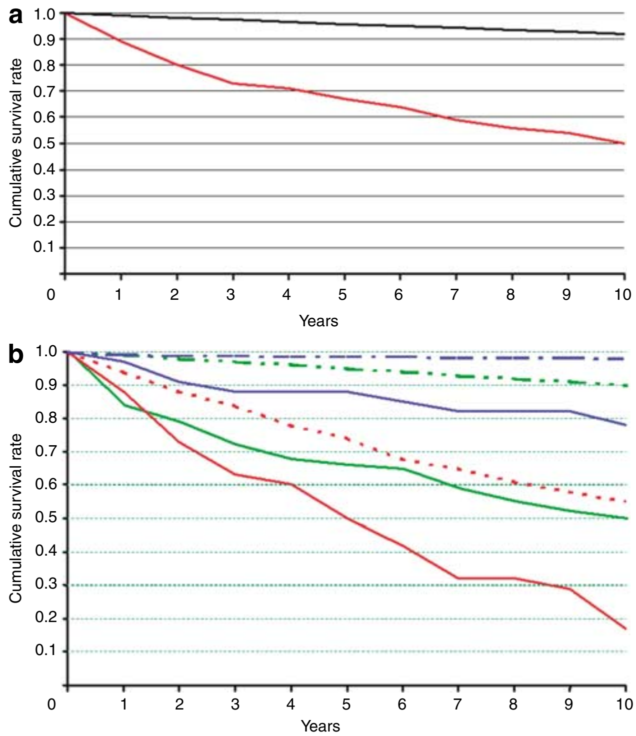

Figure 3 | (a) Graphic comparison of the survival of the patients discharged alive after an ARF episode (red line) and a cohort of all the Madrid in-habitants older than 15 years alive on 1.1.1978 (green line). (b) Graphic comparison of the effect of the age on survival in patients discharged alive after an ARF episode and that of the Madrid in-habitants alive on 1.1.1978. Solid lines represent the survival curves of the ARF patients. Discontinuous lines represent the survival curves of the Madrid inhabitants. Blue lines: people older than 30 and equal or younger than 50 years. Green lines: people older than 50 and equal or younger than 70 years. Red lines: people older than 70 years.

from 6[5] to 372[1] months; (2) the follow-up was ⩾5 years in only four articles;[1,2,8,10] and (3) only three studies included more than 150 cases.[2,9,10] Additionally, the follow-up rate in three studies is unknown or too low to obtain solid conclusions.[4,5,7] It is of note that only one epidemiological community-based study[9] and those based either on national civil register data,[2,8] or on a 'short' long-term follow-up period (12 months)[6] were able to have a hundred per cent follow-up rate. Consequently we suggest that only those articles having a follow-up period of at least 5 years, a follow-up rate near, or higher than 90% and a minimum of 100 patients followed-up should be considered for drawing conclusions on the long-term outcome of ATN.

Of patients surviving an ATN episode, 50% were still alive 10 years later. These data varied in relation to some variables. The older the age, the worse the survival rate with the exception of the youngest group of patients where acquired immunodeficiency syndrome, in the pre-retroviral era, or intravenous drug abuse was present. Also, using multivariable analysis, age was a variable having statistical influence on long-term survival. An adverse effect of age on long-term outcome of ARF patients has been previously reported.[4,7,10]

Admission type (medical, surgical, or trauma) had a significant influence on evolution, both on comparing survival curves and using multivariable analysis. The patients with better survival rates were those admitted for trauma (84% at 10 years). Cox analysis identified the type of admission as a variable with an independent predictive power; in fact, the hazard of death of surgical patients is half that of medical patients. Neither age, which was higher in surgical than in medical patients (63 ± 13 years versus 54 ± 17 years; $P = 0.000$), nor the presence of comorbidity factors (92 versus 80%, respectively in both groups) justified these findings.

As in three previous series,[7,9,10] presence of comorbidity factors in our population was associated with a worse survival rate at 10 years than that observed in patients without comorbidity factors (42% versus 85%). Although the patients having comorbidity factors were older than those with out them (60 ± 15 years versus 49 ± 20 years, respectively), the Cox proportional model clearly shows that comorbidity factors independently influence the long-term evolution (HR 4.29). When each of the 11 comorbidity factors considered was individually studied we found no significant differences in long-term survival of each group, possibly as most of the patients had more than one comorbidity factor; and the number of patients in some groups was too small to draw conclusions.

Survival at 10 years of patients needing ICU admission while presenting ARF was significantly higher than that of the patients not requiring ICU treatment (61 versus 42%, respectively; $P = 0.000$). However, this variable was not identified in survival analysis with covariants, possibly because of the influence of the other variables. In fact, among the ICU patients there was a predominance of trauma or surgical causes that were associated with a higher survival rate than that of the ARF patients admitted for medical reasons. It could be speculated that some surgical diseases and trauma lesions could be resolved by surgery, whereas medical diseases are more frequently associated with the aging process. In agreement with our findings, Morgera *et al.*[10] found that their septic patients, who had their greatest in-hospital mortality, had a tendency toward a better long-term outcome after discharge.

When we analyzed the data (not shown) of the 413 patients who developed the ARF during the inclusion period, we observed that high ISI, ICU treatment, and surgical or trauma admission were among the variables associated with a high rate of mortality in the initial evolution of the ARF. However, some variables were associated with a better probability of survival in the long-term outcome. These data suggest that an ARF developed in a severe clinical context, when the systemic inflammatory response syndrome is usually observed, is associated with initial higher mortality, but with a better long-term survival in those overcoming the clinical episode producing ARF.

As for early mortality,[13] late mortality was usually owing to the disease for which the patient was initially admitted and during which ARF developed. Similar data have been

Table 4 | Literature review: long-term outcomes of patients surviving an ARF

	Number of patients (characteristics)	Period studied	ARF etiology	Survivors (n) in-hospital mortality (%)	Maximum follow-up in months	Number of long-term studied patients	Follow-up rate	Long-term survival (%)	Functional outcome
Turney *et al.*[1a]	142 Severe ARF	1956–1987/R	Obstetric causes	112 (21%)	372	102	91%	1 year. 79%[h] 5 years: 75%[h] 10 years: 72%[h]	SCrs increased: 48%
Frost *et al.*[2b]	419 (100% dialysis)	1977–1988/R	82% ATN	226 (46%)	144	226[d] (73% ATN)	100%	Medical ARF: 52% (5 years)[g] Surgical ARF: 28% (5 years)[f]	NR
Chertow *et al.*[3b]	132 ICU setting (100% dialysis)	1991–1993/R	78% ATN	40 (70%)	12	39	97%	81%[f]	Chronic dialysis: 33%[h]
Lameire *et al.*[4b]	230 ICU setting (100% dialysis)	1993–1995/R	Most ATN	79 (66%)	18	79[e]	NA	15%[g]	NR
Brivet *et al.*[5c]	360 ICU setting (48% dialysis)	1991/P	78% ATN	150 (58%)	6	86	57%	87% (6 months)[h]	SCr ≥ 1.7 mg/dl: 28%
McCarthy *et al.*[6c]	142 ICU setting (71 patients in each period)	1977–1979 and 1991–1992/R	> 80% ATN	23 (68%)	12	23	100%	Period 77–79: 21%[g]	Period 77-79: Chronic dialysis: 4%
			> 80% ATN	37 (48%)	12	37		Period 91-92: 30%[g]	Period 91–92: Chronic dialysis: 21%
Khan *et al.*[7b]	310 (Epidemiological – community-based)	1989–1990/R	Miscellaneous	NR(?)	24	NR	NA	31% (2 years)[g]	NR
Korkeila *et al.*[8b]	62 ICU setting (100% dialysis)	1992–1993/R	ATN	34 (45%)	60	34°°	100%	35% (5 years)[g]	Chronic dialysis: 8%[g]
Stevens *et al.*[9c]	288 (Epidemiological – community-based)	1996/P	Miscellaneous	161 (56%)	36	161	100%	28% (3 years)[g]	NR
Morgera *et al.*[10b]	979 (100% CRRT)	1993–1998/R	Probably mainly ATN[f]	301 (69%)	88	267	89%	50% (5 years)[h]	Chronic dialysis: 10%[h]
Ramón y Cajal Hospital experience[a]	413 General series (48% dialysis)	1977–1992/R	ATN	187 (55%)	264	177	95%	50% (10 years)[h]	Chronic dialysis: 2%[h]

ATN, acute tubular necrosis; CRRT, continuous renal replacement therapy; ICU, intensive care unit; NA, not assessable; NR, not reported; P, prospective; R, retrospective; SCr, serum creatinine.
Follow-up rate: number of long-term followed-up patients with respect to the number of patients discharged alive.
[a]Cases with previous renal function impairment were excluded.
[b]Prior renal function unknown.
[c]Includes patients with prior renal insufficiency.
[d]Still alive according to the Danish Central Personal Register.
[e]According to the Finnish National Population Register.
[f]Personal interpretation of the authors' data.
[g]With respect to the initial population.
[h]With respect to the patients discharged alive.

reported by Frost *et al.*[2] Additionally, Gentric and Cledes[15] in a study of renal function after ATN in patients < 65 years, reported that none of their patients died owing to renal insufficiency during the long-term outcome. Although, from our data, we could not conclude whether prevention of ATN in patients with comorbid conditions could play a favorable role in the long-term outcome of this condition, it seems reasonable to implement prophylactic measures in patients in situations of risk for developing ARF.

As in other series,[11,12] renal function measured by SCr improved during the first 6 months after discharge. After that, SCr tended to stabilize, although with wide dispersion in individual values. In agreement with these data, the last clinical evaluation in 57 of our patients was satisfactory in most cases although, at some stage during the follow-up, 1.6% of the patients required dialysis treatment.

The graphic comparison of the survival curves of the ARF patients with the cohort of the whole adult population of the 1978 Madrid in-habitants discloses the importance of the long-term outcome of ARF by itself. At 10 years, the survival rate of the Madrid population was 92%, whereas that of the ARF patients was 50%. Frost *et al.*[2] compared the survival of their patients with medical or surgical ARF and that of a Danish-matched population. However their data are not directly comparable with our results as they studied the outcome from the moment of hospital admission, whereas we only considered long-term outcome of patients discharged alive after an ATN episode. The poorer survival of the ARF patients in comparison with the Madrid population cannot be attributed to age as is clearly shown in Figure 3. To the best of our knowledge this is the first time that this type of analysis has been reported.

In summary, we believe that the methodological characteristics and results of this article contribute in establishing the natural history of ARF from the introduction of renal replacement therapy by Kolff.[16] The factors conditioning the long-term outcome are age, the disease causing the initial admission at which ARF occurs, male sex, and the comorbidity factors of the patients at that time.

MATERIALS AND METHODS

Selection criteria, population, and study periods

After exclusion of patients with previous impairment of their basal renal function (SCr > 1.4 mg/dl), those who had received any kind of transplantation and those younger than 15 years, we identified 413 patients fulfilling the ATN criteria used in this article (see below). The 187 patients discharged alive constitute the population analyzed.

The inclusion period is 15 years, from October 1977, when our hospital was opened, through December 1992. The follow-up period ended on 31 December 1999. Consequently the potential observational period of the patients ranged between 7 and 22 years.

Definitions

The following concepts were defined as published previously:[13,17]

ARF was considered when a sudden rise in SCr to more than 2 mg/dl (177 μmol/l) was found in subjects with prior normal renal function.

ATN was diagnosed following an exclusion process when other possible causes of ARF were eliminated. In this article ARF is considered as synonymous with ATN.

Although *ATN etiology* is frequently multifactorial we classified our patients in one of the four following etiologic groups: (1) Surgical; (2) Nephrotoxic; (3) Septic, and (4) Medical.

Oliguria was defined as a urine output < 400 ml/24 h.

Functional severity of the ARF episode was graded as follows: (a) mild (maximum SCr $\leqslant$ 3.0 mg/dl; (b) moderate (SCr > 3.0 and $\leqslant$ 6.0 mg/dl) and, (c) severe (SCr $\geqslant$ > 6.0 mg/dl).

Recovery of renal function at hospital discharge was classified as: (a) total (SCr $\leqslant$ 1.4 mg/dl); (b) partial (SCr > 1.4 mg/dl and lower than the maximum SCr reached); and (c) absence, if the SCr was similar to the highest level observed during the ARF episode or if the patient still needed renal replacement therapy.

Renal function during the follow-up was classified as: (1) Normal (SCr $\leqslant$ 1.4 mg/dl); (2) mild renal insufficiency (SCr > 1.4 and $\leqslant$ 2.0 mg/dl); (3) moderate renal insufficiency (SCr > 2.0 and $\leqslant$ 4.0 mg/dl; (4) severe renal insufficiency (SCr > 4.0 mg/dl); and (5) terminal renal insufficiency (when chronic dialysis was needed).

Type of admission was subclassified in three categories: (1) medical (patients hospitalized for medical diseases not, at least initially, subsidiaries of surgery); (2) surgical (any admission due either to emergency or elective surgery); and (3) trauma admission.

Variables recorded during ARF admission:

(1) Sex and age; (2) comorbid conditions (cardiac, hepatic and pulmonary obstructive diseases, tumors, diabetes mellitus, hypertension, acute cerebrovascular accident, peripheral arteriopathy, aortic aneurysm, and acquired immunodeficiency syndrome); (3) ATN etiologic groups; (4) the clinical variables needed for the ISI calculation[17] at the moment when the nephrologist saw the patient for the first time; (5) need and type of dialysis: intermittent hemodialysis, peritoneal, continuous renal replacement therapies, or combinations of the previous forms; (6) the number of dialysis sessions; (7) SCr levels: at the moment of ARF diagnosis, the highest value during admission and at discharge; (8) need of ICU treatment.

During this period, severity of ARF was estimated in two ways: (1) that of the patients was calculated using the ISI,[17] whereas, (2) functional impairment was recorded as described above.

Search for long-term outcome data: operational procedure

The required information related with the long-term outcome was obtained as summarized in Figure 4. After completing all the steps in Figure 4, only 10 patients were lost to long-term follow-up; however five of them had a partial follow-up ranging between 15 and 60 days after discharge. In the case of the patients who had died outside the hospital, information about their renal function and the date and

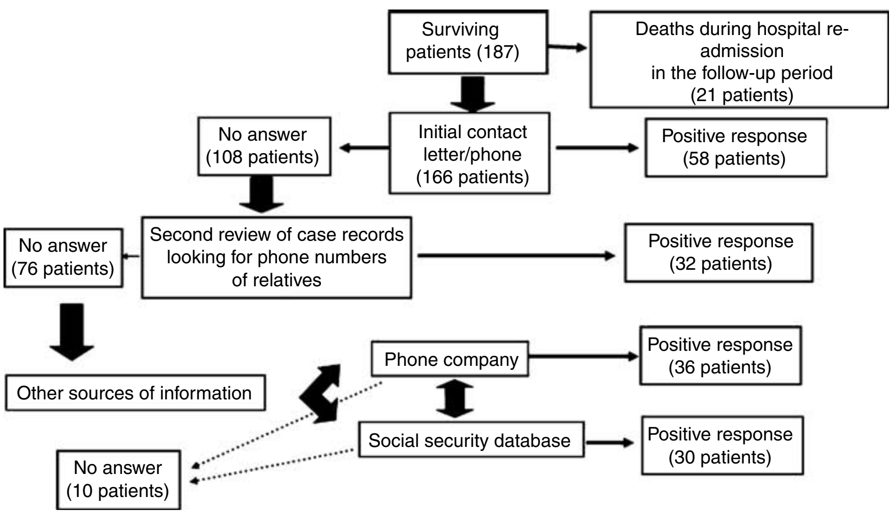

Figure 4 | Flow-chart showing the contact method and the number of patients found with each approach.

cause of death was obtained either from their relatives or their family doctors.

Management of the ARF

All patients with ATN treated in our department were seen by at least one staff member (usually FL) and one resident. In addition, all patients treated in an ICU setting were also attended by the ICU staff together with the nephrologists. Dialysis was indicated when SCr was $\geqslant 6$ mg/dl and/or blood urea nitrogen >100 mg/dl. Dialysis and/or ultrafiltration were also used to treat hyperkalemic or hypervolemic events. Supplements of water, proteins, calories, and minerals, as well as inotropic support, were individually administered as needed. The type of the dialysis membrane was not available in the case records. In general, during the first 6 years of the study cuprophanic membranes were predominant, but in the next 4 years both cuprophanic and biocompatible membranes were used, whereas during the last 5 years biocompatible membranes (polysulphone and polyacrilonitrile) were used. Usually an initial intravenous dose of 250 mg of furosemide was administered to oliguric patients.

Final clinical evaluation. All patients alive at the end of the follow-up period were requested, either during 2000 or 2001, to attend our department for a complete check-up. This evaluation included interview, physical examination and analytical tests both of blood (hemogram, glucose, uric acid, ionograme, SCr, serum urea, total proteins, and plasma osmolality) and urine (creatinine, urea, natrium, kalium, chloride, glucose, proteinuria osmolality, and urinary sediment). Additionally, Creatinine clearance was calculated by an 8-h urine collection.

Comparison of the survival rates of ARF patients and the Madrid general population. The survival curve of our patients was graphically compared with that of a cohort, the Madrid population older than 14 years, alive on 1 January 1978. This date was chosen as October 77 was the date of the inclusion of our first patient in the study. The effect of age on survival, both in ARF surviving patients and in the whole population of Madrid, was also analyzed using a similar approach. The survival curves of the normal population were performed using the Mortality Tables of the Madrid Community (years, 1978–1999) of the '*Instituto de Estadística de la Comunidad de Madrid*' (unpublished data).

Statistical analysis

Continuous variables were summarized by mean and standard deviation. Categorical variables were summarized using absolute values or proportions. Survival curves were estimated by the Kaplan–Meier method and differences between curves assessed with the log-rank test. Multivariate survival analysis was performed by the Cox model. The log-likelihood ratio test was used for model comparison and goodness of fit assessment. The final, most parsimonious model was obtained by backward selection from the maximal model composed by ten variables: age, sex, type of admission, ATN etiology, Need of dialysis, ARF functional severity, oliguria, ICU admission, level of renal function recovery at discharge, and incidence of comorbidity factors. Multinomial variables were coded by dummy variables. Statistical analysis was performed using SPSS version 10.0.

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