Renal insufficiency is an independent prognostic factor in patients with chronic lymphocytic leukemia

Among all adults, creatinine clearance decreases with age, with the majority of individuals older than 75 years having a glomerular filtration rate less than 60 mL/min.[1] In the general population, creatinine clearance levels are found to be positively associated with life expectancy. Thus survival starts to significantly decrease in patients with chronic kidney disease (CKD) stage IIIB or lower (i.e. those with a glomerular filtration rate of 45 mL/min or lower).[2] Renal function also has a well-established prognostic role in patients with selected hematologic malignancies known to impact renal function, such as multiple myeloma, where renal insufficiency (RI) affects response to alkylator-based regimens and overall survival.[3]

Chronic lymphocytic leukemia (CLL) is a disease of the elderly, with a median age at diagnosis ranging between 72 and 74 years.[4,5] As a consequence, many patients present with comorbid health conditions, including RI. However, some recent evidence suggests that, in some cases, RI may be a consequence of CLL rather than simply reflecting an aging individual.[6] We aimed to investigate the specific prognostic role of renal function in the

Table 1. Baseline characteristics and association with baseline renal insufficiency.

	RI at time of CLL diagnosis (n=103)	No RI at CLL diagnosis (n=940)	Unadjusted OR (95% CI)	Unadjusted *P*	Age- and sex-adjusted OR (95% CI)	Adjusted *P*
Median (range) age at diagnosis	82 (46-95)	64 (33-89)	6.5 (4.6-9.0)†	<0.001	–	–
Age at diagnosis (years)						
< 60	2 (2%)	361 (38%)	Reference	Reference	–	–
60-69	12 (12%)	305 (32%)	7.1 (1.6-32.0)	0.023		
70-79	31 (30%)	222 (24%)	25.2 (6.0-106.3)	0.014		
> 80	58 (56%)	52 (6%)	201.3 (47.7-849.1)	<0.001		
Male	54 (52%)	638 (68%)	Reference	0.002	–	–
Female	49 (48%)	302 (32%)	1.9 (1.3-2.9)			
No diabetes	91 (88%)	839 (91%)	Reference	Reference		
Diabetes	12 (12%)	82 (9%)	1.4 (0.7-2.6)	1.2 (0.6-2.4)		
Missing	0	19	0.36	0.65		
No HTN	44 (43%)	571 (62%)	Reference	<0.001	Reference	0.16
HTN	59 (57%)	350 (38%)	2.2 (1.4-3.3)		1.4 (0.9-2.3)	
Missing	0	19				
Median (range) ALC (x10⁹/L)	9.0 (0.5-333)	11.5 (0.4-578)	0.9 (0.8-1.1)*	0.24	1.1 (0.9-1.3)*	0.64
Median (range hemoglobin (g/dL)	12.4 (6.1-16.1)	13.9 (4.9-17.9)	0.7 (0.6-0.8)	<0.001	0.7 (0.7-0.8)	<0.001
Rai stage 0-II	85 (83%)	885 (94%)	Reference	<0.001	Reference	0.010
III-IV	17 (17%)	53 (6%)	3.3 (1.9-6.0)		2.7 (1.3-5.7)	
Missing	1	2				
CD49d						
< 45%	17 (65%)	271 (66%)	Reference	0.93	Reference	0.37
> 45%	9 (35%)	138 (34%)	1.0 (0.5-2.4)		0.6 (0.2-1.7)	
Missing	77	531				
CD38						
< 30%	48 (59%)	504 (68%)	Reference	0.09	Reference	0.19
> 30%	34 (41%)	239 (32%)	1.5 (0.9-2.4)		1.5 (0.8-2.6)	
Missing	21	197				
ZAP70						
< 20%	24 (62%)	324 (61%)	Reference	0.98	Reference	0.35
> 20%	15 (38%)	204 (39%)	1.0 (0.5-1.9)		0.7 (0.3-1.5)	
Missing	64	412				
IGHV mutated	20 (67%)	217 (48%)	Reference	0.045	Reference	0.10
Unmutated	10 (33%)	237 (52%)	0.5 (0.2-1.0)		0.5 (0.2-1.2)	
Missing	73	486				
FISH						
Normal, 13q, +12	43 (84%)	508 (85%)	Reference	0.97	Reference	0.52
11q, 17p	8 (16%)	93 (15%)	1.0 (0.5-2.2)		0.7 (0.3-1.8)	
Missing	52	339				

RI: renal insufficiency; CLL: chronic lymphocytic leukemia; OR: Odds Ratio; CI: confidence interval; n: number; HTN: hypertension; ALC: absolute lymphocyte count; FISH: fluorescence *in situ* hybridization. *Logistic models included log (ALC) due to non-normal distribution. †Per 10-year increase.

clinical outcome of patients with CLL. Here we present a retrospective analysis of the characteristics and impact of RI in a cohort of 1043 patients with newly diagnosed CLL.

The study was approved by the Institutional Review Board of Mayo Clinic and was conducted in accordance with the principles of the Declaration of Helsinki. Patients had to have a baseline pre-treatment creatinine clearance available within one year prior to or three months after CLL diagnosis. Glomerular filtration rate was calculated using the Cockroft-Gault formula. Patients with estimated glomerular filtration rate 45 mL/min or lower were classified as having RI.[2] Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA). Categorical and continuous variables were compared using the χ^2 or Fisher exact tests or the Mann-Whitney test, as deemed appropriate; unadjusted logistic regression models and age- and sex-adjusted models were then used to determine which factors were associated with RI. Survival by baseline RI status was plotted using Kaplan-Meier methods, and log-rank tests were used to compare the RI groups. Thirty-four patients were on early intervention clinical trials without treatment indications and thus were not included in the time-to-treatment analysis. RI was treated as a time-dependent variable in the analyses, and backward elimination was employed. Although we were limited by the amount of missing data, immunoglobulin heavy chain variable

Table 2. Baseline characteristics and association with acquired renal insufficiency.

	Acquired RI during CLL follow up (n=151)	No acquired RI (n=574)	Unadjusted HR (95% CI)	Unadjusted *P*	Age- and sex-adjusted HR (95% CI)	Adjusted *P*
Median (range) age at diagnosis	71 (39-87)	62 (33-85)	2.3 (2.0-2.8)†	<0.001	–	–
Age at diagnosis						
< 60	29 (19%)	249 (43%)	Reference	Reference	–	–
60-69	38 (25%)	193 (34%)	1.9 (1.2-3.1)	0.008		
70-79	67 (44%)	113 (20%)	5.5 (3.5-8.5)	<0.001		
> 80	17 (11%)	19 (3%)	11.9 (6.4-21.9)	<0.001		
Male	87 (58%)	408 (71%)	Reference	0.003	–	–
Female	64 (42%)	166 (29%)	1.6 (1.2-2.3)			
No diabetes	135 (90%)	514 (91%)	Reference	0.58	0.9 (0.5-1.5)	0.60
Diabetes	15 (10%)	49 (9%)	1.2 (0.7-2.0)			
Missing	1	11				
No HTN	92 (61%)	355 (63%)	Reference	0.32	0.8 (0.6-1.2)	0.25
HTN	58 (39%)	208 (37%)	1.2 (0.9-1.6)			
Missing	1	11	R			
Median (range) ALC (x10⁹/L)	10.4 (0.4-578)	11.2 (0.5-458)	1.0 (0.9-1.2)*	0.60	1.2 (1.0-1.3)*	0.033
Median (range) hemoglobin (g/dL)	13.5 (4.9-16.6)	14.1 (4.9-17.9)	0.8 (0.8-0.9)	<0.001	0.9 (0.8-0.9)	0.002
Rai stage						
0-II	137 (91%)	543 (95%)	Reference	0.013	Reference	0.018
III-IV	14 (9%)	29 (5%)	2.0 (1.2-3.5)		1.9 (1.1-3.4)	
Missing	0	2				
CD49d						
< 45%	27 (53%)	178 (67%)	Reference	0.034	Reference	0.11
> 45%	24 (47%)	86 (33%)	1.8 (1.0-3.1)		1.6 (0.9-2.7)	
Missing	100	310				
CD38						
< 30%	67 (60%)	330 (71%)	Reference	0.012	Reference	0.08
> 30%	44 (40%)	132 (29%)	1.6 (1.1-2.4)		1.4 (0.96-2.1)	
Missing	40	112				
ZAP70						
< 20%	35 (50%)	215 (62%)	Reference	0.040	Reference	0.055
> 20%	35 (50%)	130 (38%)	1.6 (1.0-2.6)		1.6 (0.99-2.6)	
Missing	81	229				
IGHV mutated	21 (34%)	145 (49%)	Reference	0.018	Reference	0.010
Unmutated	40 (66%)	152 (51%)	1.9 (1.1-3.2)		2.0 (1.2-3.4)	
Missing	90	277				
FISH						
Normal, 13q, +12	73 (82%)	342 (87%)	Reference	0.027	Reference	0.018
11q, 17p	16 (18%)	49 (13%)	1.9 (1.1-3.2)		2.0 (1.1-3.4)	
Missing	62	183				

RI: renal insufficiency; CLL: chronic lymphocytic leukemia; HR: Hazard Ratio; CI: confidence interval; n: number; HTN: hypertension; ALC: absolute lymphocyte count; FISH: fluorescence *in situ* hybridization. *Logistic models included log (ALC) due to non-normal distribution. †Per 10-year increase.

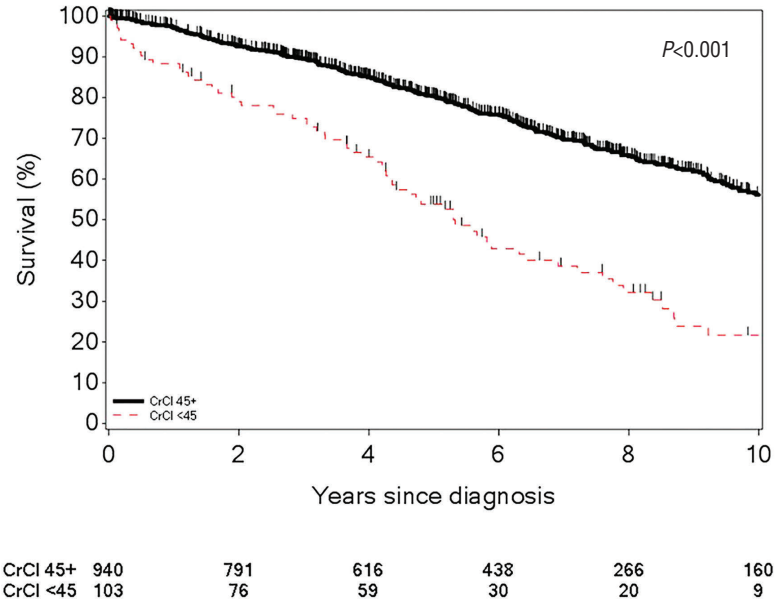

Figure 1. Overall survival by baseline renal insufficiency [RI: creatinine clearance (CrCl) < 45 mL/min].

(*IGHV*) region gene mutation status and fluorescence *in situ* hybridization (FISH) status were considered clinically important factors. Therefore, we started with the final model, which contained only significant factors, and we then ran three additional models (final + *IGHV* mutation; final + FISH; final + *IGHV* mutation + FISH) with the intention of comparing the parameter estimates for RI in the presence of *IGHV* mutation and FISH. All *P*-values were two-sided; $P \leq 0.05$ was considered significant.

One-thousand and forty-three newly diagnosed patients were included in this study and followed for a median of seven years. Baseline RI was observed in 103 (10%) patients at the time of CLL diagnosis. An additional 151 patients with normal baseline renal function at diagnosis acquired RI using an estimated glomerular filtration rate less than 45 mL/min as the defining renal function parameter during follow up for their CLL (median time to acquired RI was 15 years).

Characteristics associated with RI at the time of CLL diagnosis are shown in Table 1. After adjusting for age and sex, the factors which remained independently associated with RI at diagnosis were hemoglobin level [Odds Ratio (OR) 0.7, 95% confidence interval (CI) 0.65-0.8; *P*<0.001] and advanced Rai stage (OR 2.7, 95%CI: 1.3-5.7; *P*=0.01). Baseline characteristics associated with RI acquired during the course of follow up are shown in Table 2. When adjusting for age and sex, the factors which remained independently associated with acquired RI were hemoglobin level [hazard ratio (HR) 0.9, 95%CI: 0.8-0.95; *P*=0.002], log transformed absolute lymphocyte count [HR 1.2, 95%CI: 1.0-1.3; *P*=0.03], advanced Rai stage (stage III-IV) (HR 1.9, 95%CI: 1.1-3.4; *P*=0.02), unmutated *IGHV* (HR 2.0, 95%CI: 1.2-3.4; *P*=0.01), and high-risk FISH (deletion 17p or deletion 11q *vs.* other FISH) (HR 2.0, 95%CI: 1.1-3.4; *P*=0.02).

After a median follow up of seven years, 436 patients progressed to require treatment. In univariate analysis, baseline RI was not associated with time-to-first treatment (TTFT) (*P*=0.57). Among the 436 patients who progressed to require treatment, 359 had creatinine clearance values available at treatment initiation. Of note, patients with RI at the start of therapy more frequently received a non-purine analog alkylator-based regimen (70% *vs.* 29.5%) rather than a purine analog-based regimen (6.7% *vs.* 48.6%) (*P*<0.001). Among 118 patients who received an alkylator-based regimen as first-line treatment (i.e. were treated similarly), overall survival after therapy did not differ significantly based on whether patients did or did not have RI at the time of treatment (HR 1.6, 95%CI: 0.9-2.8; *P*=0.14).

After a median follow up of seven years, 382 patients have died. Median overall survival (OS) for the overall cohort was ten years. During follow up, 25 (2% of overall cohort) patients required dialysis (4 when in end-stage renal disease, 21 during an event of acute kidney injury); however, none received a kidney transplant. On univariate analysis, both baseline RI (Figure 1) and time-dependent RI were associated with a shorter OS (both *P*<0.001). The association between RI and OS persisted on multivariable analysis adjusting for age, sex, diabetes, hemoglobin levels, Rai stage, FISH and *IGHV* status (HR 2.6, 95%CI: 1.9-3.4; *P*<0.001). Importantly, RI remained a significant predictor of OS when high-risk FISH and/or *IGHV* mutation status were also included in the models (*P*<0.001).

We present here the first analysis of the prevalence, characteristics and prognostic significance of RI in a large cohort of patients with newly diagnosed CLL. In our study, 10% of patients had RI at time of CLL diagnosis, and an additional 151 patients later acquired RI during the course of the disease, highlighting the relatively high prevalence of this condition. After adjusting for age and sex, only the hemoglobin level and Rai III-IV stage were associated with RI at the time of CLL diagnosis. In a relevant finding, we recently published a series of 49 patients with monoclonal-B-cell lymphocytosis (MBL) or CLL who had undergone a renal biopsy because of RI or the nephrotic syndrome. Up to 90% of pathology findings were either directly (infiltration) or indirectly (infection-associated) related to CLL, highlighting the apparent patho-biological relationship between CLL and renal function in some patients.[6]

In the present cohort, RI was also acquired during the course of CLL follow up in an additional 151 patients. After adjusting for age and sex, factors associated with acquired RI during follow up included advanced Rai

stage, del17p or del11q by FISH and unmutated *IGHV*. Unfavorable prognostic factors are typically found to be associated with more aggressive disease and increase the need for treatment. Thus, the latter findings are consistent with an association between high-risk prognostic parameters and acquired RI.

We found that RI influences the type of therapy received where the majority of patients with RI requiring treatment received alkylator-based regimens rather than purine nucleoside analog-based regimens as first-line therapy. This observation is to some extent expected, since purine nucleoside analogs are metabolized by the kidney and are more difficult to administer in RI. In contrast to what is observed amongst patients with multiple myeloma,[3,7] CLL patients in our study who received an alkylator-based regimen and had RI had similar survival to patients treated with an alkylator-based regimen who did not have RI.

Finally, RI was associated with OS, in both univariate and multivariable analyses. Several studies have found an association between comorbidities and survival in CLL, although renal function was either not included or not analyzed individually in these reports.[8,9] Our data reveal that RI appears to have an independent prognostic role in patients with CLL. Given this, we would propose that the impact of RI as a prognostic comorbid feature warrants validation in prospective studies, along with other previously recognized comorbidities.[10]

In conclusion, we find that RI is a relatively common condition in patients with CLL, with 24% of newly diagnosed CLL experiencing RI at some point during their disease course. RI in patients with CLL can affect both treatment selection and survival, and validation of RI as an independent prognostic factor in prospective studies is warranted.

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doi:10.3324/haematol.2016.150706

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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