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Chronic lymphocytic leukemia in Oman: real-world outcomes, molecular testing gaps, and access to targeted therapy in a low- incidence setting

Salim Al Ruqeishi
Sultan Qaboos University Hospital
Vinodh Kumar
Sultan Qaboos University Hospital
Mahmood Al Abri
Sultan Qaboos University Hospital
Ibrahim Al Nabhani
Sultan Qaboos University
Khalil Al Farsi
khalilf@squ.edu.om

Sultan Qaboos University Hospital

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Abstract

Background

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western populations but is uncommon across the Arabian Peninsula, where real-world outcome data and information on care-delivery gaps remain sparse. We describe the clinical profile, treatment patterns, long-term outcomes, and the system-level care gaps that shaped them, in Omani patients diagnosed with CLL at a national tertiary referral center.

Methods

We conducted a retrospective observational cohort study including all adults with confirmed CLL managed at Sultan Qaboos University Hospital (SQUH), Muscat, between January 2010 and December 2020. Risk classification relied on combined Binet/Rai stage, since IGHV mutational analysis and TP53 sequencing were not available locally during the study period and FISH was non-uniform. Kaplan–Meier methods were used for overall survival (OS) and progression-free survival (PFS); Cox proportional hazards regression was conducted as an exploratory analysis given the limited number of events.

Results

Forty-nine patients were included in survival analyses; baseline data were complete for 48. The median age at diagnosis was 62 years (range 32–90) and 62.5% were men, younger than the Western median of around 70–72 years and consistent with neighboring Gulf series. Overall, 28 patients (57.1%) required therapy; chemoimmunotherapy accounted for 85.7% of first-line regimens and only 14.3% received a Bruton tyrosine kinase (BTK) inhibitor. The proportion of treated patients receiving front-line CIT was identical in 2010–2015 and 2016–2020 (84.6% in each half), suggesting that local treatment patterns lagged behind the global pivot to chemotherapy-free regimens. After a median follow-up of 44.7 months (treated patients 65.4 months), the estimated median OS from diagnosis was 167 months (95% CI, 153 months–not reached), with a 5-year OS of approximately 85%; survival data remain immature. Median PFS from first-line therapy was 52.3 months. In an exploratory Cox model, age ≥ 65 years at diagnosis was associated with markedly inferior OS (hazard ratio 11.43; 95% CI, 2.06–63.60; P = .005); the wide confidence interval reflects the small number of events.

Conclusions

In this first published Omani CLL cohort, long-term survival appeared broadly comparable with international benchmarks despite limited access to molecular risk stratification and targeted therapy during the study period. Older patients experienced substantially inferior survival. The findings establish

a chemoimmunotherapy-era baseline and highlight the need for national CLL pathways that incorporate IGHV/TP53 testing and equitable access to chemotherapy-free regimens.

Background

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in North America and Western Europe, with an age-adjusted incidence of approximately 4.5 to 4.8 per 100,000 per year in the United States [1, 3] and roughly comparable rates across most of high-income Europe. The epidemiologic picture is markedly different across much of the rest of the world. In East Asia, CLL is distinctly uncommon, and in the Arab populations of the Gulf the disease appears at a fraction of the Western rate. Published data from Kuwait, where a long-running tertiary cancer center captures most of the country's incident cases, suggest a crude annual incidence of around 0.4 per 100,000 [4], and a single-center experience from the United Arab Emirates identified only 37 CLL patients seen across five years at the country's largest cancer center [5]. Oman has not, to our knowledge, published a national CLL incidence figure; however, the very small number of cases reaching the country's main academic referral center each year, set against a national population of approximately four million during the study period [29], is consistent with a similarly low burden. The contrast with Western incidence rates is therefore at least an order of magnitude [1, 3, 4].

Whether this low apparent incidence reflects true biological differences, a younger age structure of the underlying population, underdiagnosis, or some combination of these, remains debated. What is clearer is that the clinical phenotype may not simply mirror that of Western cohorts. Regional reports describe a younger median age at diagnosis (approximately 59–62 years versus around 70–72 years in Western series), a male predominance broadly similar to the West, and a somewhat different distribution of FISH-detected abnormalities, with lower rates of del(13q) and TP53 aberrations in some series [4, 5, 7]. Against this backdrop, practical questions about diagnosis, staging, and treatment in low-incidence settings tend to be answered by extrapolation from European and North American guidelines [1, 2], because the local evidence base is thin.

The treatment landscape for CLL has shifted substantially over the past decade. Chemoimmunotherapy (CIT) with regimens such as fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine and rituximab (BR) was the standard of care for fit patients through the early 2010s [11, 12], with chlorambucil-based approaches reserved for older or less fit individuals. The approval and uptake of Bruton tyrosine kinase (BTK) inhibitors, and later BCL2 inhibitors, progressively displaced CIT from the front-line setting in high-income countries [13–16, 23]. Across the Gulf, access to these agents has been variable and generally delayed, and reimbursement pathways have only recently matured. Published Saudi consensus guidelines now explicitly favor targeted therapy in the front-line setting [6], but a large fraction of patients treated during the 2010s in the Arabian Peninsula received CIT [7].

Beyond the choice of regimen, the iwCLL framework now relies on molecular tools — immunoglobulin heavy chain variable region (IGHV) mutational status and TP53 disruption — to allocate patients between

CIT and chemotherapy-free pathways [2, 18, 22]. Where these tests are unavailable, risk stratification rests on clinical staging alone, which is known to be less discriminating than integrated indices such as the CLL-IPI [10]. This is a salient gap in low-incidence, resource-constrained settings, and is one of the reasons why outcomes data from such settings carry particular value: they describe what actually happens to patients managed without the full molecular toolkit.

Oman is a useful lens through which to examine these issues. It is a middle-income Gulf country with a young population (median age in the mid-20s for much of the study window [29]), a universal public health system, and a small number of tertiary hematology services. Sultan Qaboos University Hospital (SQUH) functions as both a national academic referral center and a routine secondary care provider for a large catchment area [9]. Outcomes data from this setting have not been published. In this study we ask three questions about CLL care in Oman during 2010–2020: how do Omani patients with CLL present clinically; what outcomes did they achieve in an era dominated by chemoimmunotherapy and limited molecular diagnostics; and which care-delivery gaps most plausibly limit further improvement?

Methods

Study design and setting

This was a retrospective observational cohort study carried out at Sultan Qaboos University Hospital, a 540-bed academic tertiary center in Muscat that houses one of only two national hematology-oncology training programs in Oman. The hospital provides diagnostic hematopathology, immunophenotyping, conventional cytogenetics, FISH, and the full range of CLL-directed therapies that were available in the country during the study period. Reporting followed the STROBE statement for observational studies [27].

Patients and case ascertainment

We included all consecutive adult patients (≥18 years) with confirmed CLL or small lymphocytic lymphoma (SLL) actively managed at SQUH between January 1, 2010 and December 31, 2020. The diagnosis in every patient was made according to the iwCLL criteria in force at the time of diagnosis [2], with immunophenotypic confirmation (CD5+, CD19+, CD23+ clonal B-cell population) on peripheral blood or bone marrow. Patients diagnosed elsewhere or earlier and subsequently followed at SQUH during the study window were eligible if their diagnostic material and records were available for review; consequently, dates of original diagnosis spanned 2003 to 2021, although all patients contributed follow-up time during 2010–2020. We excluded patients with insufficient baseline documentation to permit staging and those whose follow-up consisted of a single visit only. Forty-nine patients met inclusion criteria and were included in survival analyses; one patient had incomplete baseline staging data, leaving 48 patients for the descriptive baseline characteristic comparisons reported in Table 1.

Staging and risk classification

Both Rai and Binet staging systems were used in clinical notes during the 11-year study window, reflecting evolving local practice. To allow uniform analysis we mapped each patient to a single combined stage variable (stages 0–IV), aligning Rai 0 with Binet A (early/asymptomatic), Rai I–II with Binet B, and Rai III–IV with Binet C. We then derived a three-tier clinical risk classification (low, intermediate, high) on the basis of this combined stage. We did not calculate the CLL International Prognostic Index (CLL-IPI) [10], because two of its required inputs (IGHV mutational status and TP53 disruption) were not available as clinical tests at SQUH during the study period. Our classification of "high risk" should therefore be understood as a purely clinical category (combined Rai/Binet stage III–IV equivalent) and not as a molecularly defined high-risk group in the contemporary iwCLL sense [2,18,22].

Data collection

Two investigators independently extracted data from the hospital's electronic medical record and, where necessary, from archived paper charts. Variables collected included age at diagnosis, sex, combined stage at presentation, complete blood count and lactate dehydrogenase at diagnosis, beta-2 microglobulin where recorded, FISH results, indication for therapy, first-line and subsequent regimens, date of any documented progression or relapse, date of last follow-up, and vital status. Risk categories (low, intermediate, high) were assigned on the basis of combined Binet/Rai stage as described above [10,26].

Two laboratory gaps deserve explicit mention. IGHV mutational status was not available as a clinical test at SQUH during the study period [18], and targeted TP53 sequencing was likewise not performed routinely [22]. FISH for the CLL panel (del(13q), del(11q), del(17p), and trisomy 12) was available but was not obtained uniformly [17]. Where patients had been assessed elsewhere, external reports were captured when present. Cause of death was not systematically captured: there is no established cause-of-death database at the institutional level, and we did not have a reliable way to classify deaths as CLL-related versus non-CLL-related. We therefore did not analyze cause-specific mortality.

Outcomes and definitions

The primary outcome was overall survival (OS), defined as the time from CLL diagnosis to death from any cause, with censoring at last documented follow-up. Progression-free survival (PFS) was evaluated in patients who received first-line therapy, defined as the time from the start of first-line treatment to documented progression or death, whichever came first. Time to first treatment (date of first-line therapy minus date of diagnosis) was abstracted but proved unreliable on quality review: in a substantial fraction of treated records the documented date of first-line therapy preceded the documented date of diagnosis, most plausibly because patients were diagnosed and partially managed externally before being registered formally at SQUH, or because of date-entry inconsistencies in the historical record. Because

the field could not be reconciled retrospectively without access to outside-hospital records, we did not analyze time to first treatment formally; this is acknowledged as a limitation.

Statistical analysis

Continuous variables are reported as means with standard deviations and medians with interquartile ranges; categorical variables are reported as counts and percentages. Between-group comparisons used the independent-samples t-test for continuous variables and the chi-square or Fisher exact test for categorical variables, as appropriate. Kaplan–Meier curves were used to estimate OS and PFS, with 95% confidence intervals calculated using the log-log transformation; differences between groups were tested with the log-rank test. Median follow-up was estimated by the reverse Kaplan–Meier method.

A Cox proportional hazards regression model was constructed to estimate hazard ratios (HRs) for OS as a function of age category (<65 versus ≥65 years), sex, and combined risk group (low–intermediate versus high). Because only 10 deaths were observed across the cohort, this multivariable model included three covariates and is best regarded as exploratory; the events-per-variable ratio is below the conventional threshold of 10 and the resulting estimates carry wide confidence intervals [2,10]. Proportional hazards assumptions were inspected graphically and with Schoenfeld residuals, and no clear violations were identified. All analyses were performed in R version 4.5.3 (R Foundation for Statistical Computing, Vienna, Austria) using the survival and survminer packages [28]. Two-sided P values <.05 were considered statistically significant.

Results

Patient characteristics

Across the 11-year study window, 49 patients met inclusion criteria; baseline data adequate for full descriptive comparison were available in 48. This corresponds to approximately 4–5 CLL patients managed per year at the center, consistent with the broader picture of CLL as an uncommon disease in the Gulf [4,5]. Table 1 summarizes baseline characteristics for the whole cohort and stratified by treatment status (watch-and-wait versus treated).

The median age at diagnosis was 62 years (range 32–90; interquartile range 52–70), with a mean of 61.7 years (standard deviation 13.2). Just over sixty percent of patients were younger than 65 at diagnosis, and 37.5% were 65 or older. The cohort was male-predominant (62.5% men; male-to-female ratio approximately 1.7:1). Stage at presentation was heterogeneous: 27.1% had stage 0 disease, 16.7% stage I, 14.6% stage II, 29.2% stage III, and 12.5% stage IV. When aggregated into clinical risk groups, 27.1% were low risk, 31.2% intermediate, and 39.6% high risk.

As expected from the way treatment decisions are made in CLL [2], the watch-and-wait and treated subgroups differed markedly in disease burden. All 20 watch-and-wait patients had stage 0 or I disease

at diagnosis, and none were classified as clinically high risk. In contrast, among the 28 treated patients, 25 of 28 (89.3%) presented with stage II–IV disease and 67.9% were classified as clinically high risk. Age distribution and sex were broadly similar between the two groups (P = .659 and .545, respectively).

Table 1. Baseline characteristics of CLL patients at Sultan Qaboos University Hospital, 2010–2020

Characteristic	Overall (N=48)	Watch & Wait (n=20)	Treated (n=28)	P value
Age at diagnosis (years)				.659‡
Mean (SD)	61.7 (13.2)	62.7 (11.8)	61.0 (14.3)	
Median (range)	62.0 (32–90)	60.0 (45–90)	62.5 (32–82)	
Age category, n (%)				1.000†
<65 years	30 (62.5)	13 (65.0)	17 (60.7)	
≥65 years	18 (37.5)	7 (35.0)	11 (39.3)	
Sex, n (%)				.545†
Female	18 (37.5)	9 (45.0)	9 (32.1)	
Male	30 (62.5)	11 (55.0)	19 (67.9)	
Combined Rai/Binet stage, n (%)				<.001†
Stage 0	13 (27.1)	13 (65.0)	0 (0)	
Stage I	8 (16.7)	7 (35.0)	1 (3.6)	
Stage II	7 (14.6)	0 (0)	7 (25.0)	
Stage III	14 (29.2)	0 (0)	14 (50.0)	
Stage IV	6 (12.5)	0 (0)	6 (21.4)	
Clinical risk group, n (%)				<.001†
Low	13 (27.1)	13 (65.0)	0 (0)	
Intermediate	15 (31.2)	7 (35.0)	8 (28.6)	
High	19 (39.6)	0 (0)	19 (67.9)	

Abbreviations: SD, standard deviation. Risk classification was based on combined Rai/Binet clinical stage; molecular risk markers (IGHV, TP53) were not available locally during the study period. Percentages may not sum to 100 because of rounding. ‡Independent-samples t-test. †Chi-square or Fisher exact test.

Cytogenetics and molecular work-up

Among the 28 treated patients, FISH results were available in 24 (85.7%), with abnormalities identified in 17 and normal results in 7; four assays had failed or were not performed. Of the 17 patients with a positive FISH result, the most common finding was trisomy 12, reported in 12 (70.6%); del(13q) was noted in 2, del(17p) in 1, and other findings in the remaining 2. Although trisomy 12 appeared frequent among patients with abnormal FISH, the denominator was small and FISH testing was non-uniform across the cohort; this finding should therefore be considered hypothesis-generating only [17]. The absence of IGHV and TP53 data also means that patients with high-risk molecular features may not have been fully identified [18,22].

Treatment patterns and the CIT-era context

Twenty-eight patients (57.1% of the cohort) received therapy during follow-up; the remaining 20 (40.8%) were observed throughout and did not meet treatment criteria by the closing date. Median age at first-line therapy was 61.5 years (range 32–81). Chemoimmunotherapy dominated the first-line landscape: 24 of 28 treated patients (85.7%) received CIT, while 4 (14.3%) received a BTK inhibitor. Within the CIT group, the regimens used were bendamustine–rituximab (BR) in 13 patients [12], fludarabine–cyclophosphamide–rituximab (FCR) in 7 [11], and chlorambucil with rituximab in 4. The pattern is largely a calendar effect: most treatment episodes occurred in the first half of the decade, before BTK inhibitors had become widely accessible in Oman, and most older or frailer patients received chlorambucil-based regimens. Detailed treatment characteristics, response patterns, and outcomes among treated patients are summarized in Table 2.

To probe whether front-line treatment selection shifted over time, we compared patients diagnosed in the first half of the study window (2010–2015) with those diagnosed in the second half (2016–2020). Among treated patients with a year of diagnosis falling in either half (n = 26 of 28), the proportions were strikingly similar: 11 of 13 patients diagnosed in 2010–2015 (84.6%) and 11 of 13 diagnosed in 2016–2020 (84.6%) received first-line CIT, and only 2 of 13 in each era (15.4%) received a front-line BTK inhibitor. Front-line treatment selection at SQUH therefore did not measurably shift toward chemotherapy-free regimens between the first and second halves of the decade, despite the global pivot to BTK inhibitors as standard of care that occurred during the same period [13,14]. This stagnation is itself a finding: it suggests that, in our setting, the bottleneck was not clinician awareness but a delayed translation of international evidence into local formulary access.

Table 2. Treatment patterns and outcomes among treated patients (n = 28)

Variable	Value
Median age at first-line therapy, years (range)	61.5 (32–81)
Sex (male), n (%)	19 (67.9)
Clinical high-risk at start of therapy, n (%)	19 (67.9)
First-line regimen, n (%)	
Chemoimmunotherapy (CIT), all	24 (85.7)
Bendamustine–rituximab (BR)	13 (46.4)
Fludarabine–cyclophosphamide–rituximab (FCR)	7 (25.0)
Chlorambucil + rituximab	4 (14.3)
BTK inhibitor (front-line)	4 (14.3)
FISH performed prior to therapy, n (%)	24 (85.7)
Abnormal FISH result	17 (60.7)
Trisomy 12 (among abnormal)	12/17 (70.6)
del(17p) (among abnormal)	1/17 (5.9)
IGHV mutational status performed	0 (0)
TP53 sequencing performed	0 (0)
Median follow-up from start of therapy, months (95% CI)	65.4 (38.8–118.0)
Documented progression or relapse, n	10
Deaths during follow-up, n (% of treated)	7 (25.0)
Median PFS from first-line therapy, months (95% CI)	52.3 (48.0–NR)
Median OS from first-line therapy, months (95% CI)	76 (63.1–NR)

Abbreviations: BTK, Bruton tyrosine kinase; CI, confidence interval; CIT, chemoimmunotherapy; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable region; NR, not reached; OS, overall survival; PFS, progression-free survival. Formal iwCLL response categories (CR/PR/SD/PD) were not consistently documented in the medical record across the study window and are therefore not tabulated here.

Survival outcomes

Median follow-up for the whole cohort, estimated by the reverse Kaplan–Meier method, was 44.7 months (95% CI, 34.9–85.8); among treated patients it was 65.4 months (95% CI, 38.8–118.0). Ten

deaths were observed across the whole cohort (20.4%), 7 of which occurred among treated patients. Cause of death was not systematically captured in our setting (see Limitations), and we therefore did not classify deaths as CLL-related versus non-CLL-related.

The estimated median OS for the whole cohort from the time of diagnosis was 167 months (95% CI, 153 months–not reached), with a 5-year OS of approximately 85% and a 10-year OS of approximately 68% (Figure 1). The 167-month figure should be interpreted with appropriate caution: median follow-up was 44.7 months, only 10 deaths had occurred at data cut-off, and the right-hand portion of the curve is supported by very few patients. The data therefore remain immature, and the median OS estimate is likely to be revised downward as further events accrue. Within the treated subgroup, median OS from the start of first-line therapy was 76 months (95% CI, 63.1 months–not reached), and median PFS was 52.3 months (95% CI, 48.0 months–not reached) (Figures 4 and 5). Roughly 35–40% of treated patients had progressed or died by 60 months from the start of therapy.

Age at diagnosis had a clear impact on survival. Patients aged <65 years had a markedly better OS than those aged ≥65 years, with estimated 5-year survival of approximately 95% versus approximately 65%, respectively, and a median OS not reached in the younger group compared with around 68 months in the older group (log-rank P = .00072; Figure 2).

In an exploratory Cox model (Figure 3), age ≥65 years was associated with markedly inferior OS (HR 11.43; 95% CI, 2.06–63.60; P = .005). The magnitude of this effect should be interpreted cautiously: only 10 deaths were observed across the cohort, the events-per-variable ratio is below the conventional threshold of 10, and the upper bound of the confidence interval is wide. Male sex was not associated with survival (HR 1.22; 95% CI, 0.30–5.00; P = .785), and clinically defined high-risk stage showed a point estimate in the expected direction but did not reach statistical significance (HR 1.80; 95% CI, 0.47–6.93; P = .393), consistent with limited statistical power.

Discussion

This is, to our knowledge, the first published cohort describing the clinical profile and long-term outcomes of CLL in Oman. Across an 11-year window at the country's main academic tertiary center, only 49 patients were identified, a figure broadly in keeping with reports from neighboring Gulf states [4,5] and consistent with the view that CLL is a rare disease in the Arabian Peninsula. The low absolute numbers translate into meaningful practical challenges: clinicians see relatively few CLL patients per year, molecular diagnostics do not always justify a dedicated in-country workflow, and regional evidence to guide management decisions is limited [6,7]. Within those constraints, the outcomes we observed (an estimated median OS approaching 14 years from diagnosis for the whole cohort) appeared broadly comparable to international benchmarks [1], although follow-up is modest and the long-tail estimate should be interpreted as provisional.

Why is the Omani cohort younger?

The median age at diagnosis in this cohort (62 years) is roughly a decade below the Western median of around 70–72 years [1,24] and is closely aligned with the Kuwaiti experience (median 59 years) [4] and the UAE experience (median 59 years) [5]. Two non-exclusive explanations have been offered in the regional literature. The first is demographic: the Omani national population had a median age of approximately 25–28 years during the study window [29], and the older age strata are numerically small, so the absolute number of CLL diagnoses in those strata will be correspondingly small even if the age-specific incidence rate matches that of the West. The second is biological: it has been suggested that earlier disease onset in some lymphoid malignancies in Arab populations may reflect genuine differences in genetic risk or environmental exposure [8]. Our data cannot adjudicate between these explanations because we lack denominator-population age structure data and IGHV mutational status; however, the consistency of the younger median age across multiple Gulf cohorts argues that the finding is real, regardless of mechanism, and should inform clinical expectations in the region.

The age signal: an honest reading

The most striking feature of our analysis was the strong association between age ≥65 years at diagnosis and inferior OS, with a point estimate of around 11 in the exploratory Cox model. Three caveats apply. First, the confidence interval is wide (2.06–63.60), which means the magnitude is poorly estimated even though the direction is clear. Second, the events-per-variable ratio (10 deaths, 3 covariates) is below the conventional threshold for stable multivariable estimation. Third, age and comorbidity are entangled: older CLL patients have more competing risks, tolerate CIT less well [21], and (in our cohort, particularly before BTK inhibitors were widely available) had fewer therapeutic options. A similar age effect has been described in the Kuwaiti cohort, where a CLL-specific comorbidity index that accounts for both chronological age and organ function performed better than age alone as a survival predictor [8]. The interpretation we favor is therefore conservative: older patients in this Gulf cohort fared substantially worse, the effect is biologically plausible, but the precise magnitude requires confirmation in larger regional series. Pragmatically, older Gulf patients with CLL should be a priority group for expanded access to chemotherapy-free regimens [13,15].

A CIT-era cohort: implications and a baseline for what comes next

The treatment pattern in this cohort reflects a specific moment in CLL history. Only 4 patients (14.3% of treated) received a BTK inhibitor in the front line; 86% were treated with chemoimmunotherapy. By contemporary standards (including the most recent regional guidelines in the Gulf [6]) this proportion would be much higher. Two forces drove the pattern we saw. First, the bulk of treatment episodes occurred before BTK inhibitors were reimbursed and routinely accessible in Oman; second, treating physicians during this period had extensive experience with FCR and BR in younger fit patients [11,12], and the local formulary favored those agents. The median PFS of 52.3 months we observed with

predominantly CIT-based therapy is in the range reported by international cohorts treated with BR or FCR [11,12], and is a reassuring signal that treatment delivery at SQUH was broadly adherent to the standard of care in its era. The contemporary reader should, however, interpret this figure in historical context: front-line continuous BTK inhibitor therapy delivered substantially longer PFS in randomized trials [13,14], and the balance of evidence now favors targeted therapy for fit patients, particularly for those with del(17p) or TP53 aberration [6,22]. Our cohort is best understood, therefore, as a CIT-era baseline against which future Omani cohorts treated in the BTK and venetoclax era can be measured. Setting that baseline is itself useful: without it, future improvements would be impossible to attribute to changes in practice.

A more uncomfortable observation emerges from the calendar-era comparison. The proportion of treated patients receiving front-line CIT was identical in 2010–2015 and in 2016–2020 (11 of 13 in each era, 84.6%), despite the latter half of the decade overlapping with the publication and incorporation into international guidelines of practice-changing trials of front-line ibrutinib and ibrutinib–rituximab [13,14]. In other words, although the global treatment landscape shifted decisively toward chemotherapy-free regimens during the second half of the study window, treatment patterns at SQUH did not move with it. Some of this lag is undoubtedly explained by the small absolute numbers of patients diagnosed each year, which limits the ability to detect a shift, but the more substantive explanation is access. Until BTK inhibitors were brought into the national formulary in Oman, awareness of their evidence base did not translate into prescribing. This is a familiar pattern in low-incidence, resource-constrained settings, and is precisely the type of access-driven gap that warrants attention in regional and global cancer care delivery.

Molecular testing gaps and the iwCLL guideline disconnect

The absence of IGHV mutational analysis and routine TP53 sequencing during the study period is a limitation of the manuscript that is, more importantly, a limitation of clinical practice in the setting at the time. Both tests are now firmly embedded in the iwCLL framework: IGHV because it separates patients with a long natural history from those who do poorly with CIT [18,19], and TP53 because del(17p) or TP53 mutation should mandate a chemotherapy-free regimen rather than CIT [2,22]. Without these inputs, the CLL-IPI cannot be calculated [10], and risk stratification falls back on clinical staging, which under-discriminates patients with biologically aggressive but clinically early disease. The fact that neither test was routinely available in Oman until very recently is not unique to this country; similar gaps have been documented from several Middle Eastern and North African centers [6,7]. The implication for guideline adherence is direct: a strict reading of iwCLL recommendations could not be achieved at SQUH during the study period for any patient, because the prerequisite molecular data were not in hand. Plans are now in place to incorporate IGHV mutational analysis and TP53 sequencing into the diagnostic workflow at SQUH through a combination of in-country capacity building and use of regional reference laboratories; future cohorts will therefore be assessable with the contemporary risk framework.

Care-delivery gaps and proposed solutions

Synthesizing the foregoing observations, four care-delivery gaps emerge as priorities for CLL care in Oman, summarized in Table 3 alongside concrete proposed solutions. Each is, in our view, addressable on a realistic time horizon and at modest cost relative to the clinical impact.

Table 3. Care-delivery gaps in CLL management in Oman and proposed system-level interventions

Care gap	Observed issue	Clinical impact	Proposed solution
Molecular diagnostics	No routine IGHV mutational analysis or TP53 sequencing during the study period; FISH non-uniform	Risk-adapted therapy not feasible; CLL-IPI cannot be calculated; iwCLL guideline adherence limited	Establish national or GCC-regional reference laboratory; integrate IGHV/TP53 into the standard CLL diagnostic pathway
Targeted therapy access	Only 14.3% of treated patients received a front-line BTK inhibitor; the proportion was unchanged between 2010–2015 and 2016–2020 (15.4% in each half)	Older or unfit patients and patients with TP53 aberration may receive CIT against current guidance; lag between evidence and access	National formulary pathway prioritizing TP53-aberrant disease, older/unfit patients, and relapsed/refractory disease for BTK inhibitor or venetoclax-based therapy
Registry and epidemiology	Single-center cohort of 49 patients over 11 years; no published Omani CLL incidence figure	Limited national epidemiologic understanding; outcome benchmarks unstable; small cohorts cannot answer biological questions	Establish a national CLL dataset linked to the Oman National Cancer Registry; pursue a pooled GCC CLL registry to reach analytic numbers comparable to mid-sized European series
Case ascertainment and referral	Single tertiary center captures the cohort; possible underdiagnosis of indolent disease	Possible underestimation of disease burden; late presentation in some patients with high-risk stage	Strengthen primary-care pathways for evaluation of unexplained lymphocytosis; develop a national CLL referral protocol

Abbreviations: BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; CLL-IPI, CLL International Prognostic Index; FISH, fluorescence in situ hybridization; GCC, Gulf Cooperation Council; IGHV, immunoglobulin heavy chain variable region; iwCLL, International Workshop on CLL.

Cytogenetic patterns: a hypothesis-generating signal

Our FISH findings (a high apparent rate of trisomy 12 among positive cases and relatively few del(13q) findings) are broadly consistent with a pattern that has been described in some other Middle Eastern

cohorts, though not in all of them [5]. Interpreting this pattern from 17 positive cases is hazardous, and the Kuwaiti series, which is substantially larger, reported del(13q) in 31% and trisomy 12 in 22% [4], closer to the Western pattern [17] than to ours. Whether our distribution represents a true regional difference, a selection artifact (FISH was non-uniform), or simple sampling noise cannot be resolved here, and the finding should be regarded as hypothesis-generating only. Confirmation in a pooled GCC CLL registry would be a natural next step.

Limitations

The limitations of this study are those common to single-center retrospective reports in rare diseases. The sample size is small, driven by the genuine rarity of CLL in Oman rather than by narrow eligibility criteria, and the number of events is correspondingly modest, which limits the precision of our survival estimates and the power of our multivariable models. With 10 deaths and three covariates, the Cox regression should be regarded as exploratory; we have flagged this throughout. We did not have access to IGHV or TP53 sequencing, and FISH was not uniform; prognostic classification therefore rests on clinical staging, which is known to be less discriminating than the CLL-IPI [10]. Time to first treatment could not be analyzed reliably because the documented date of first-line therapy preceded the documented date of diagnosis in a substantial fraction of records, most plausibly reflecting external diagnosis with later registration at SQUH or historical date-entry inconsistencies that we could not reconcile. Cause of death was not systematically captured; in the absence of an established cause-of-death database, we did not attempt to classify deaths as CLL-related versus non-CLL-related. Formal iwCLL response categories (CR/PR/SD/PD) were inconsistently documented in the medical record across the study window. The calendar-era comparison was descriptive and not powered to detect modest shifts in practice. Our findings reflect a single tertiary academic hospital, and although SQUH draws from a wide catchment area, a national registry-based analysis would paint a fuller picture. Finally, the treatment era captured here predates the routine use of BTK and BCL2 inhibitors in Oman, and the outcomes observed should not be taken as a prediction of outcomes in patients being treated today [6,13,15,23].

Conclusion

In this first published Omani CLL cohort, long-term survival appeared broadly comparable with international benchmarks despite limited access to molecular risk stratification and targeted therapy during the study period. Older patients experienced substantially inferior survival. The findings establish a chemoimmunotherapy-era baseline against which future Omani cohorts treated with BTK and BCL2 inhibitors can be measured, and they highlight four concrete care-delivery priorities: integration of IGHV and TP53 testing into the diagnostic pathway, equitable formulary access to chemotherapy-free regimens, a national CLL dataset linked to the Oman National Cancer Registry, and strengthened primary-care evaluation of unexplained lymphocytosis. None of these priorities is unique to Oman;

together they form a template for CLL care improvement across low-incidence, resource-constrained settings.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Medical Research Ethics Committee of the College of Medicine and Health Sciences, Sultan Qaboos University, Muscat, Oman (Reference No. SQU-EC/472/2021; MREC #2482). Because of the retrospective design and the use of de-identified clinical data extracted from existing medical records, the requirement for individual written informed consent was waived by the same committee. The study was conducted in accordance with the principles of the Declaration of Helsinki and with the institutional standards governing the protection of patient privacy and the confidentiality of medical records. All data were anonymized prior to analysis.

Consent for publication

Not applicable. The manuscript does not contain any individual person's identifying data.

Availability of data and materials

The de-identified datasets analyzed during the current study are available from the corresponding author on reasonable request and subject to institutional approval.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KF conceived and designed the study. SR and KF collected and assembled the data. KF performed the data analysis and interpretation. SR and KF drafted the manuscript. VK, MA, and IN contributed to the interpretation of clinical data and critical revision of the manuscript. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Figures

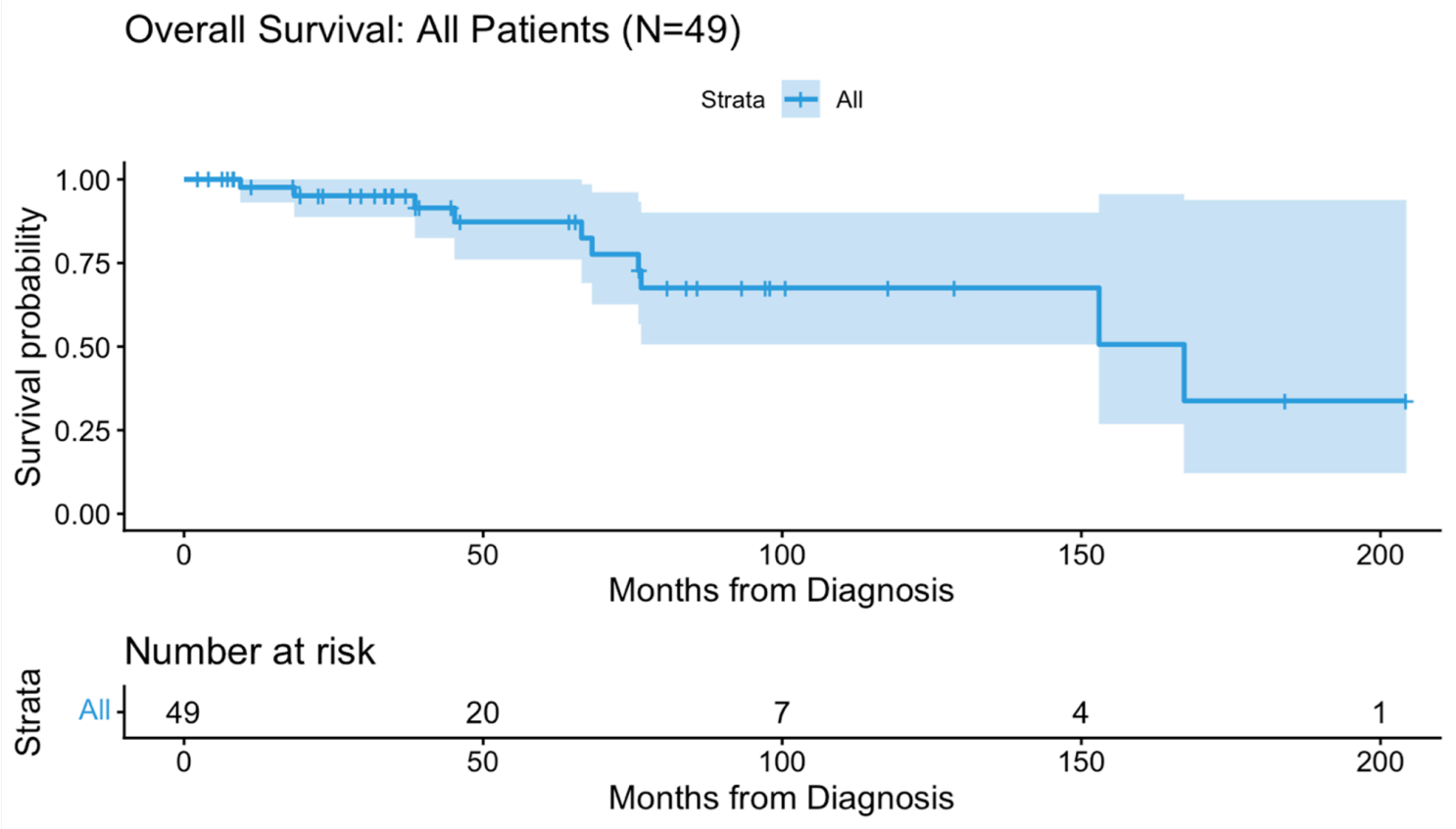


Figure 1

Kaplan–Meier estimate of overall survival from diagnosis for the entire CLL cohort (N = 49). The estimated median overall survival was 167 months (95% CI, 153–not reached); this estimate is provisional given the median follow-up of 44.7 months and only 10 deaths. Tick marks indicate censored observations; the shaded band represents the 95% confidence interval. The risk table below the x-axis shows the number of patients at risk at each time point.

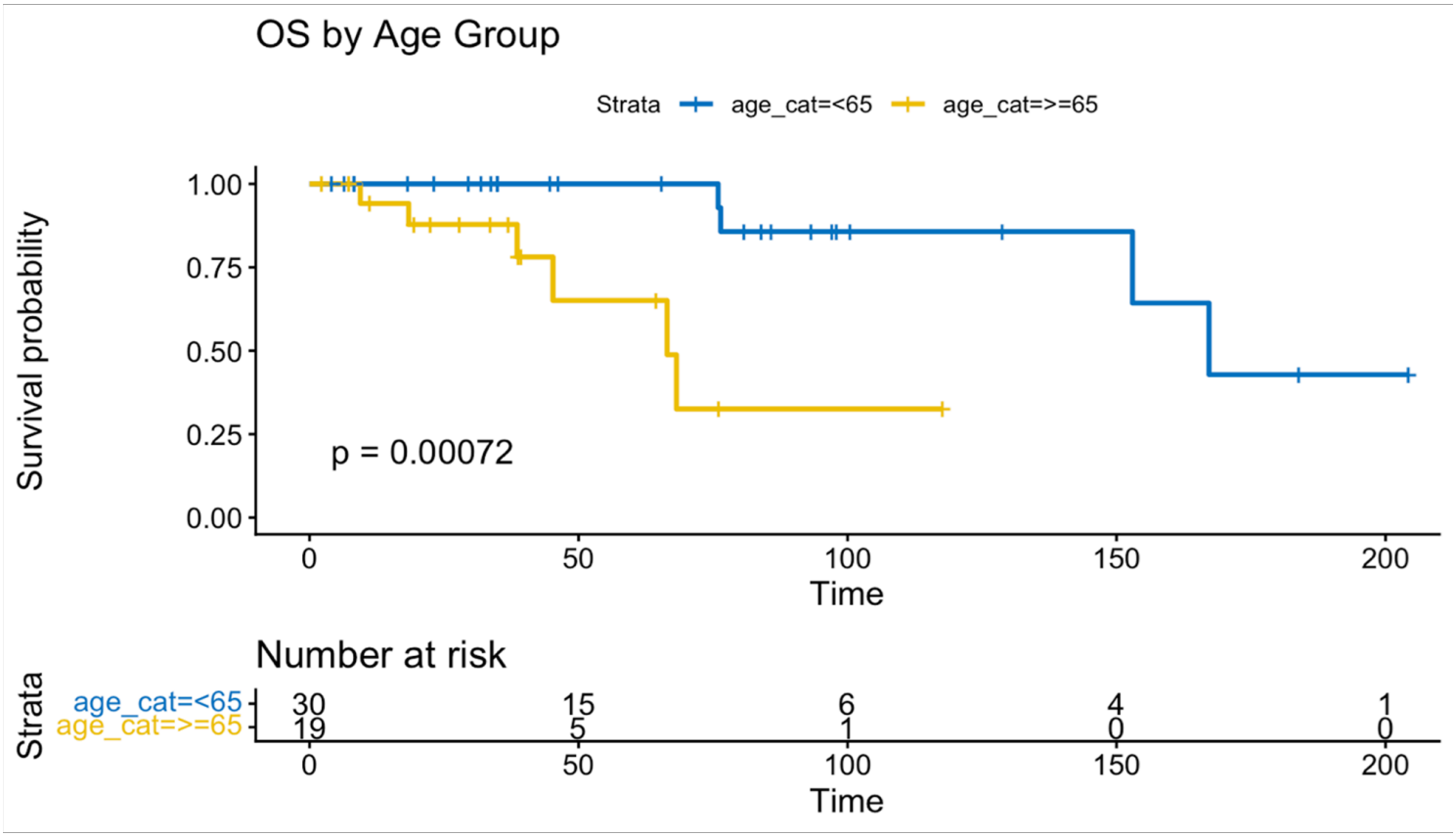


Figure 2

Overall survival stratified by age group at diagnosis. Patients <65 years (blue) had substantially better survival than patients ≥65 years (yellow); log-rank P = .00072. Risk tables below the x-axis show the number of patients at risk in each stratum at the indicated time points.

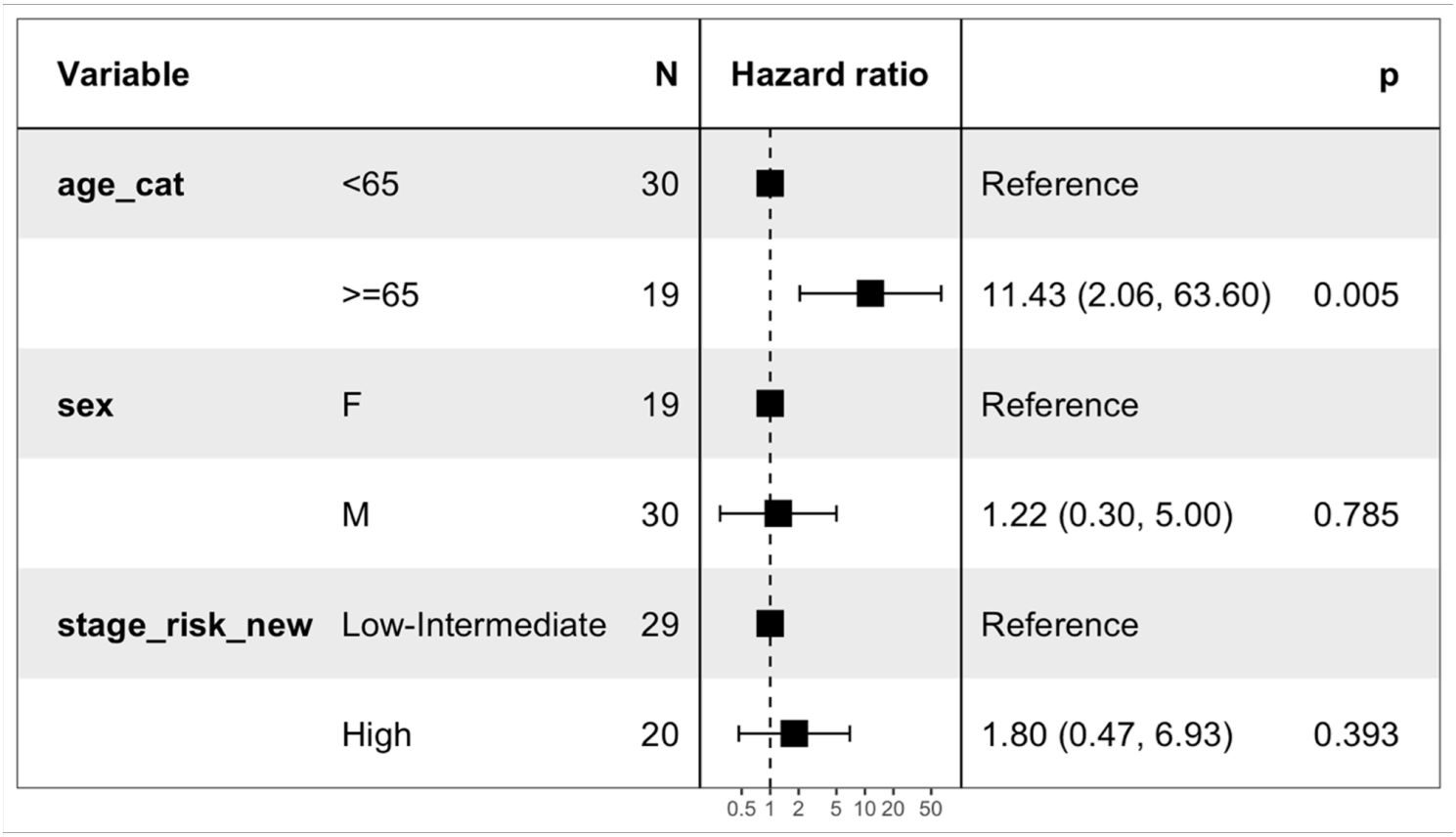


Figure 3

Forest plot of hazard ratios from the exploratory Cox proportional hazards model for overall survival. Age ≥65 years at diagnosis was the only variable independently associated with inferior OS; sex and clinically defined high-risk stage were not significantly associated with OS. Point estimates and 95% confidence intervals are shown on a log scale.

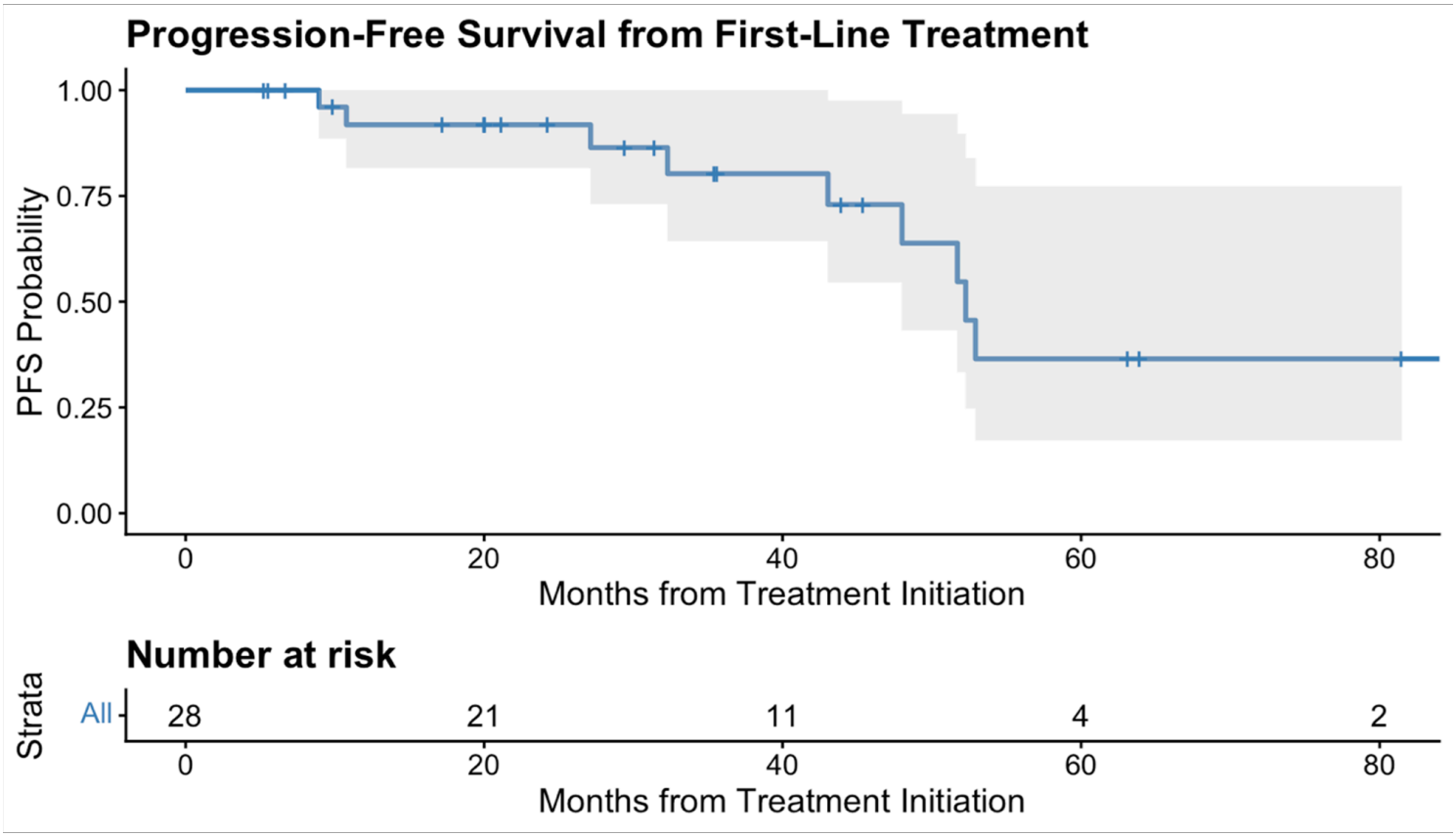


Figure 4

Progression-free survival from the start of first-line therapy in treated patients (n = 28). Median PFS was 52.3 months (95% CI, 48.0–not reached). Tick marks indicate censored observations; the risk table below the x-axis shows the number of patients at risk at each time point.

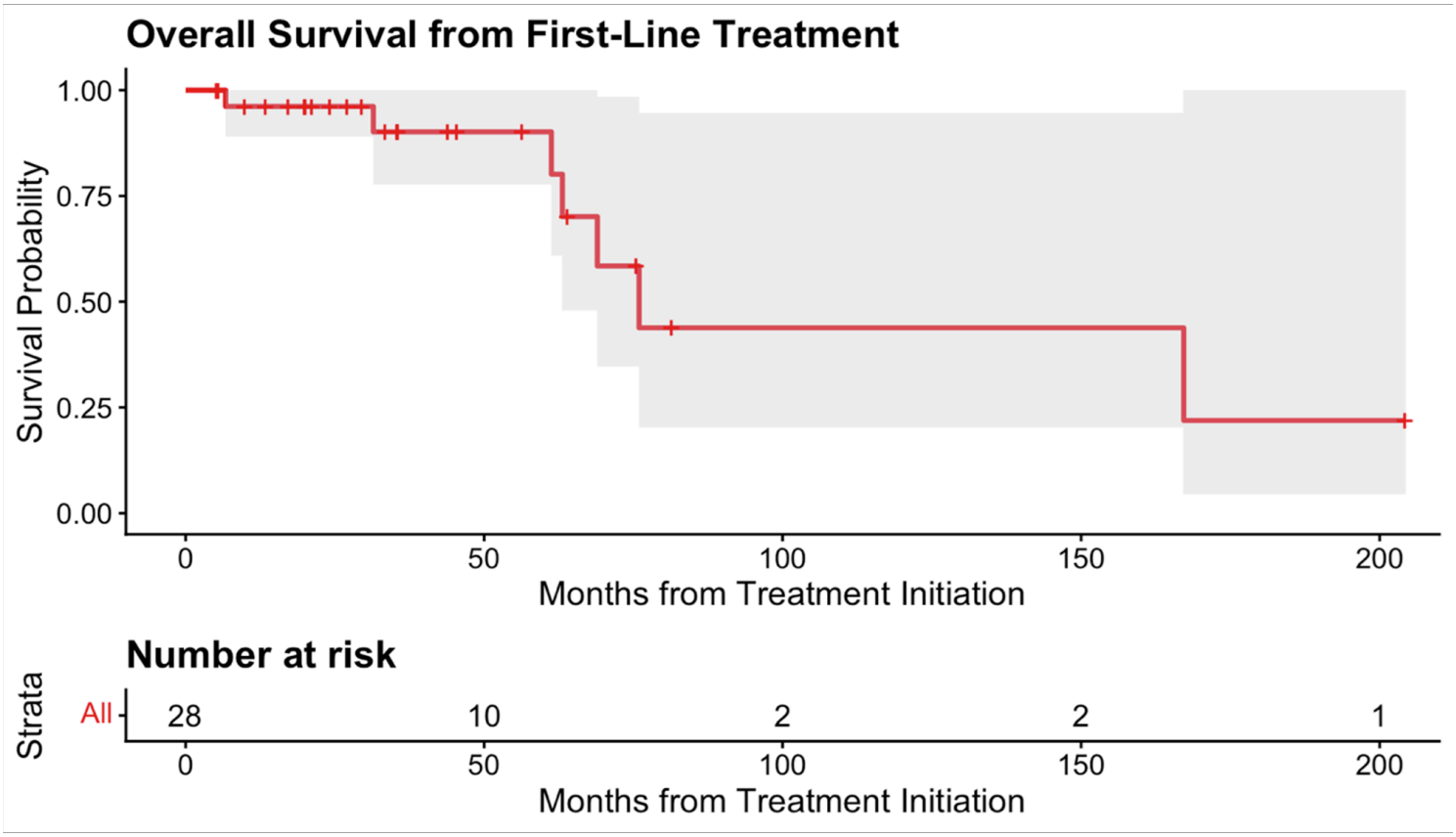


Figure 5

Overall survival from the start of first-line therapy in treated patients (n = 28). Median OS from treatment initiation was 76 months (95% CI, 63.1–not reached). Tick marks indicate censored observations; the risk table below the x-axis shows the number of patients at risk.