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Authors

Gordon, Max
Kaempf, Andy
Sitlinger, Andrea
et al.

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The chronic lymphocytic leukemia comorbidity index (CLL-CI): a three-factor comorbidity model

Max J. Gordon[#1], **Andy Kaempf**[#2], **Andrea Sitlinger**[3], **Geoffrey Shouse**[4], **Matthew Mei**[4], **Danielle M. Brander**[3], **Tareq Salous**[5], **Brian T. Hill**[5], **Hamood Alqahtani**[6], **Michael Choi**[6], **Michael C. Churnetski**[7], **Jonathon B. Cohen**[7], **Deborah M. Stephens**[8], **Tanya Siddiqi**[4], **Xavier Rivera**[9], **Daniel Persky**[9], **Paul Wisniewski**[10], **Krish Patel**[10], **Mazyar Shadman**[11], **Byung Park**[#2], **Alexey V. Danilov**[#2,4]

[1]Oregon Health & Science University, Portland, OR, USA,

[2]Knight Cancer Institute, Portland, OR, USA,

[3]Duke Cancer Institute, Durham, NC, USA,

[4]City of Hope Comprehensive Cancer Center, Duarte, CA, USA,

[5]Cleveland Clinic, Cleveland, OH, USA,

[6]Moores Cancer Center at UC San Diego, San Diego, CA, USA,

[7]Winship Cancer Institute, Emory University, Atlanta, GA, USA,

[8]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA,

[9]University of Arizona, Tucson, AZ, USA,

[10]Swedish Cancer Center, Seattle, WA, USA,

[11]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[#] These authors contributed equally to this work.

Abstract

Purpose: Comorbid medical conditions define a subset of chronic lymphocytic leukemia (CLL) patients with poor outcomes. However, which comorbidities are most predictive remains understudied.

Experimental Design: We conducted a retrospective analysis from 10 academic centers to ascertain the relative importance of comorbidities assessed by the Cumulative Illness Rating Scale (CIRS). The influence of specific comorbidities on event-free survival (EFS) was assessed in this derivation dataset using random survival forests to construct a CLL-specific comorbidity index (CLL-CI). Cox models were then fit to this dataset and to a single-center, independent validation dataset.

Corresponding authors: Alexey V. Danilov, City of Hope National Medical Center, 1500 E Duarte Rd, Duarte, CA 91010. tel. 626-256-4673, adanilov@coh.org. Byung Park, Oregon Health and Science University, 2720 SW Moody Ave, Portland OR 97201. Tel. 503-418-0127, parkb@ohsu.edu.

Results: The derivation and validation sets comprised 570 patients (59% receiving Bruton tyrosine kinase inhibitor [BTKi]) and 167 patients (50% receiving BTKi), respectively. Of the 14 CIRS organ systems, three had a strong and stable influence on EFS: any vascular, moderate/severe endocrine, moderate/severe upper gastrointestinal comorbidity. These were combined to create the CLL-CI score, which was categorized into 3 risk groups. In the derivation dataset, the median EFS was 58, 33, and 20 months in the low, intermediate, and high risk groups, correspondingly. Two-year overall survival (OS) rates were 96%, 91%, and 82%. In the validation dataset, median EFS was 81, 40, and 23 months (two-year OS rates 97%/92%/88%), correspondingly. Adjusting for prognostic factors, CLL-CI was significantly associated with EFS in patients treated with either chemo-immunotherapy or with BTKi in each of our 2 datasets.

Conclusions: The CLL-CI is a simplified, CLL-specific comorbidity index which can be easily applied in clinical practice and correlates with survival in CLL.

Keywords

CLL; comorbidities; cumulative illness rating scale; machine learning

Introduction

Chronic lymphocytic leukemia (CLL) is a common leukemia with variable clinical course. Part of this variability can be explained by concurrent medical problems, which are frequently present (1). The impact of comorbidities on overall survival (OS) of CLL patients has been shown to be comparable to the negative impact of a complex karyotype (2). To highlight the importance of comorbidities, the International Workshop on CLL 2018 guidelines recommend systematic assessment of comorbidities in patients enrolled on clinical trials (3).

Comorbidities in CLL have been assessed using different clinical tools. By far the most commonly used is the Cumulative Illness Rating Scale (CIRS). CIRS is a rigorous tool designed initially to evaluate the impact of comorbidities in hospitalized geriatric patients (4). In CLL, CIRS has been used extensively in major past and ongoing clinical trials as part of inclusion criteria and for baseline demographic assessment (5–9). Our group and others have demonstrated that CIRS score predicts survival in patients with CLL treated with either chemo-immunotherapy (CIT) or ibrutinib, a Bruton tyrosine kinase inhibitor (BTKi), independent of biologic factors (2,10,11). However, some studies did not endorse its predictive value in patients treated with CIT (12) or phosphoinositide-3 kinase inhibitor idelalisib (13). Furthermore, due to complexities in scoring, CIRS has not become part of routine clinical practice. Meanwhile, general scales which measure comorbidities, for example the Charlson comorbidity index, have not consistently demonstrated a correlation with survival in patients with CLL or have correlated with OS but not CLL-specific OS (1,14,15).

Herein, we investigated the relative impact of specific CIRS categories on survival in CLL and propose a new CLL comorbidity index (CLL-CI). The simplicity of this new CLL-CI could facilitate the objective measure of comorbidities in clinical practice.

Methods

Patient eligibility

For the derivation dataset, patient data was obtained from 10 academic medical centers in the United States following approvals by the respective institutional review boards. Patients who received treatment for CLL between 2000 and 2019 were included in this analysis. Four patients received first treatment prior to then. A single-institution validation dataset included 167 patients treated at the City of Hope National Medical Center between 2009 and 2020. Patients with Richter's transformation were excluded. Electronic medical records were retrospectively reviewed to determine patient characteristics at the time of treatment initiation, including age, performance status, cytogenetics, prior treatments, and comorbidities. For the validation set, only comorbidity data pertaining to the three organ systems previously selected for CLL-CI were collected.

Assessment of comorbidities by CIRS

Comorbidities were evaluated based on documentation of medical problems, aided by review of medications in the patients' medical record. CIRS score was calculated for each patient at the time of treatment initiation as in Salvi et al. (4). Each organ system (e.g. endocrine, cardiac, etc.) was rated for severity of impairment or dysfunction on a scale of 0–4 (0 = normal organ function; 1 = mild comorbidity; 2 = moderate comorbidity; 3 = severe comorbidity; 4 = extremely severe comorbidity). The vascular/hematopoietic category was modified to omit "hematologic malignancy" and only evaluated other comorbidities within this system since all patients in this study had CLL. Additionally, medical conditions which were deemed complications of CLL, e.g. anemia, thrombocytopenia, or splenomegaly, were not included as part of the total CIRS score. In keeping with previous studies which have applied CIRS to CLL, patients were deemed to have high comorbidity burden if total CIRS score was at least 7 (CIRS ≥7) (6–9).

Statistical Methods

Derivation set EFS outcomes were modeled with random survival forests (RSF's). Predictor variables in these models included the 14 CIRS organ classes (recoded from 0–4 to 0–3 by merging scores 3 and 4 because of sparse numbers of observed 4's), treatment setting (frontline vs relapsed/refractory [R/R]), treatment type (CIT vs kinase inhibitor), del(17p)/*TP53* mutation, and age. Each variable's strength of association with EFS was assessed using two RSF outputs: (1) variable importance (VI), computed by calculating the decrease in a survival tree's predictive accuracy (based on Harrell's concordance index) when a variable of interest is randomly permuted, then averaging this change in prediction error across all trees in the forest and (2) minimal depth (MD), computed as the tree-averaged shortest distance between a specific tree's root node and the first node that uses a variable of interest to partition the data and create two new branches (16–20).

Each forest had an average of 15 observations per terminal node of a tree and comprised 10,000 trees. Because each recoded CIRS variable could be dichotomized at 3 different values, 3 random splits were considered for each variable in the node-specific, randomly chosen variable set of size 5 [= ceiling(√18)], with the best split identified as the value

yielding the largest log-rank test statistic (21,22). The 18 variables – 14 CIRS classes plus the 4 aforementioned prognostic factors – were ranked by VI and MD, separately, with lower numbered ranks representing higher VI values (i.e., variables with a greater contribution to predicting EFS) and lower MD values (i.e., variables possessing best splits closer to root nodes, thus partitioning more patients according to EFS).

The reliability of RSF output was evaluated by stratifying the dataset on the historical prognostic factors and randomly selecting 100 different sub-samples, each two-thirds the size of the full dataset, and fitting an RSF to each sub-sample (with the same RSF parameters as described above). CIRS-specific VI rank and MD rank distributions across these 100 random sub-samples were compared so that the variable selection decision could take into account internal consistency of RSF results. This RSF reliability was also assessed by totaling the number of times each CIRS variable was included in a VI rank or MD rank "top x" set, with x=[3,4,5,6], per the clinical desire to reduce the number of utilized CIRS variables while retaining prognostic information.

Upon selecting a subgroup of CIRS variables with convincing association with EFS (in the presence of known prognostic factors), the most common split point for each chosen CIRS variable was identified by extracting node information from all 10,000 trees. Since splits partition the observations at a given node into a left daughter node (≤ split value) and a right daughter node (> split value) and since each CIRS variable was coded 0 to 3, possible split values were 0, 1, and 2. This practice of identifying the most common split points was also applied to each of the 100 sub-sample RSF's in order to assess variability. When there was no clearly superior split point for a specific CIRS variable, split values that created a small subgroup when applied to the full dataset were discounted because survival estimates based on fewer patients are more volatile and less likely to be reproduced in an orthogonal dataset.

Once the most common (and thus optimal, in terms of discriminating patients based on EFS) split points were determined, a CLL-CI score was constructed by assigning 1 point if the observed value of a particular CIRS variable was greater than the corresponding optimal split value and then summing these points across the set of chosen CIRS variables. The final categorical CLL-CI was formed from the continuous score after collapsing adjacent values pertaining to smaller numbers of patients.

In both datasets, EFS was defined as the number of months from initiating CLL treatment to the earliest of the following events: any evidence of disease progression or recurrence (including development of new CLL-related symptoms), start of a new therapy, death. Overall survival (OS) was defined as the number of months from treatment initiation to death. Patients with no observed EFS or OS events were censored at last follow-up. The Kaplan-Meier method and log-rank test were used to estimate and compare survival curves for comorbidity groups without considering other patient or disease characteristics. Multivariable Cox proportional hazard regression was utilized for modeling EFS and OS in each of the datasets, separately, to (i) create adjusted (i.e., prognostic factor balanced) survival curves for specific comorbidity groups and (ii) estimate adjusted hazard ratios and associated Wald test p-values for each model predictor (23,24). Gonen-Heller concordance probability estimates were computed for Cox multivariable models and were considered

when evaluating the discriminative effect of including cardiac and hypertension CIRS categories in the CLL-CI, in the context of derivation set ibrutinib patients (25,26). The concordance probability is the chance that, for a randomly selected pair of patients, the patient with the higher model-estimated risk of the outcome actually experienced the event first. Patient-level differences between the 3 CLL-CI groups were evaluated with Kruskal-Wallis and Fisher's exact tests. P-values <0.05 were considered statistically significant. R version 4.0.2 was used to perform all statistical analyses and create all figures.

Results

Patient characteristics

Our derivation set consisted of 570 patients with complete data for the 14 CIRS organ system variables and the 4 known prognostic factors (Table 1). The median age was 67 years (range 30–91). Del(17p) and/or *TP53* mutation was present in 114 patients (20%). ECOG performance status was ≥2 in 36 patients (6%) and missing in 51 (9%). Median CIRS score was 7 (range 0–29) with CIRS≥7 (indicating high comorbidity burden) in 302 patients (53%). Three hundred and one patients (53%) were assessed in the R/R setting. Ibrutinib was the most commonly prescribed treatment (n=339, 59%), followed by fludarabine and bendamustine. Median follow-up was 31 months (interquartile range [IQR] 13–49, range 1–328), with 106 observed deaths (19% of patients). Forty-eight percent of patients experienced an EFS event during follow-up.

CIRS comorbidities

In our derivation dataset, the most frequently encountered comorbidities of any degree by CIRS organ system were endocrine (n=294, 52%), hypertension (n=279, 49%), musculoskeletal (n=269, 47%), and respiratory (n=215, 38%). Severe (CIRS grade 3–4) comorbidities were most frequently encountered in the hypertension (n=115, 20%), vascular (n=50, 9%), cardiac (n=49, 9%), and psychiatric/behavioral (n=41, 7%) categories. A complete list of comorbidities by CIRS organ class and grade are displayed in Supplemental Table 1.

Random survival forest modeling for variable and split selection

When fitting an RSF to the complete derivation set of 570 patients, endocrine, vascular, and upper gastrointestinal had the 3 highest importance scores as well as the 3 smallest minimal depths. These organ systems were the only CIRS variables to outperform the 4 known prognostic factors on both RSF measures of influence. Across the 100 random sub-samples (each with n=380 patients), the VI rank and MD rank distributions exhibited a clear separation between endocrine, vascular, and upper gastrointestinal (GI) and the remaining CIRS classes (Fig. 1A–B). Furthermore, when the top 3 CIRS variables were identified for each sub-sample (according to each RSF metric separately), endocrine and vascular were included in this top set in 80 or more of the 100 samples for both VI and MD (Fig. 1C–D). Upper GI eclipsed the 80% mark for MD top 3 inclusion while still making the VI top 3 in about half of the 100 sub-samples (Fig. 1C–D). The highest top 3 inclusion percentages among other CIRS variables by RFS measure were: musculoskeletal at 22% for VI and renal at 11% for MD. As endocrine, vascular, and upper GI were ranked 1→2→3 for both VI and

MD and demonstrated consistent rankings across random samplings of the derivation cohort, these CIRS variables were selected for comorbidity scoring that was applied to both of our datasets.

In order to utilize RSF tree structure and nodal splitting information (providing the variable and split point that maximized the log-rank statistic and, hence, the difference in EFS between the resulting two daughter nodes) to construct a CLL comorbidity score, the most common split for the 3 top performing CIRS variables were: split value =1 for endocrine, split value =0 for vascular, and split value =1 for upper GI. An upper GI split value of 2 was about as common as the chosen value of 1 but was downweighted since the derivation set had only 9 cases of severe comorbidities (CIRS grade 3–4) in this class. Thus, regarding a patient's particular CIRS values, 1 point was assigned for each of the following conditions: endocrine >1 (moderate-to-severe comorbidity), vascular >0 (mild-to-severe) and upper GI >1 (moderate-to-severe). Within each patient, points were summed up and the resulting score categorized as follows to create a three-group CLL-CI: 0 points = low risk, 1 point = intermediate risk, 2–3 points = high risk. Examples of medical conditions in the 3 chosen CIRS categories, as described in Salvi et al. (4), as well as instructions on how to score and categorize the CLL-CI can be found in Table 2.

The CLL-CI independently correlates with survival

Applying the new CLL-CI scoring system to the derivation dataset of 570 patients, there were 226 (40%) low risk, 233 (41%) intermediate risk, and 111 (19%) high risk patients. The percentage of patients with CIRS≥7 in each CLL-CI group was 23% for low risk, 64% for intermediate risk, and 90% for high risk.

Using the CLL-CI score, the median EFS was 58 months (95% CI: 46–108) in low risk, 33 months (95% CI: 28–41) in intermediate risk, and 20 months (95% CI: 14–32) in high risk patients (log-rank $p<0.001$; Fig. 2A). In comparison, median EFS was 55 months for CIRS<7 (95% CI: 47–68) and 25 months for CIRS≥7 (95% CI: 23–32; log-rank $p<0.001$; Supplemental Fig. 1A).

When adjusting for known prognostic factors (treatment setting, treatment type, age at treatment initiation, and del(17p)/*TP53* mutation) in multivariable Cox models, a greater CLL-CI-defined comorbidity burden was associated with inferior EFS (Table 3; intermediate vs. low HR=1.83, $p<0.001$; high vs. intermediate HR=1.45, $p=0.015$; Fig. 2B). Additionally, older age, R/R status, and treatment with CIT were each associated with reduced EFS (Supplemental Table 2). Although not reaching statistical significance, *TP53* aberrations were also associated with inferior EFS (HR=1.33; $p=0.073$). ECOG performance status was not included in the multivariable models as it was not a significant predictor of EFS in this setting and was missing in 9% of patients. However, when ECOG was added as a Cox model covariate, CLL-CI retained its strong correlation with EFS (intermediate vs. low HR=1.94, $p<0.001$; high vs. intermediate HR=1.41, $p=0.041$).

Estimated OS rate at 2 years was 95.8% in low risk, 90.5% in intermediate risk, and 81.5% in high risk CLL-CI (log-rank $p<0.001$; Fig. 2C). By comparison, 2-year OS rates were 97.0% for CIRS<7 and 85.1% in patients with CIRS ≥7 (log-rank $p<0.001$; Supplemental

Fig. 1C). When adjusting for known clinical predictors in a Cox model, higher CLL-CI was associated with increased chance of death (intermediate vs. low HR = 1.51, p=0.091; high vs. intermediate HR = 1.61, p=0.048; Fig. 2D). Similar to EFS, receiving treatment in the R/R setting (HR=1.84, p=0.017), older age (HR=1.24 for each 5-year increase, p<0.001), and harboring a *TP53* aberration (HR=1.94, p=0.006) were associated with decreased survival. Treatment with a kinase inhibitor (i.e. ibrutinib [n=339] or idelalisib [n=10]), as opposed to CIT, did not correlate with OS (HR=1.39, p=0.268). This was not surprising given the relatively short follow-up of patients treated with ibrutinib (median 23 months, range 1–71) and is consistent with findings in randomized trials comparing ibrutinib to CIT (27,28).

Additionally, we tested the CLL-CI in several key subgroups (Fig. 2E–H, Supplemental Fig. 2). When evaluated in Cox models alongside clinical prognostic factors, CLL-CI remained an independent predictor of reduced EFS in patients treated with CIT (n=221; Table 3) and in patients receiving ibrutinib (n=339; intermediate vs. low HR=1.65, p=0.024; high vs. intermediate HR=1.70, p=0.018). Also, from multivariable Cox modeling, the CLL-CI-defined comorbidity burden was independently associated with inferior EFS in both frontline and R/R settings. In models of OS that controlled for clinical predictors, patients with high risk CLL-CI had significantly worse OS than patients with intermediate risk CLL-CI in the subgroup of frontline patients (n=269, HR=2.71, p=0.009). In addition, there were trends toward shorter survival with each increasing CLL-CI category within the 3 other subgroups defined by disease setting or treatment (Table 3).

Comorbidities in ibrutinib-treated patients

Patients receiving ibrutinib formed the largest treatment cohort in this analysis (n=339 in the derivation dataset). Ibrutinib discontinuation rates due to adverse events were more frequent in patients with high (21%, n=142) and intermediate risk CLL-CI (29%, n=63) compared to those with low risk CLL-CI (13%, n=134). However, there was no correlation between CLL-CI comorbidity level and ibrutinib dose reduction (high=22%, intermediate=25%, low=21% of patients requiring at least one dose reduction).

Among patients treated with ibrutinib, the distributions of Rai stage and *IGHV* mutational status (the latter available for 164 patients [48.4%]) were similar between the three CLL-CI groups and neither was significantly associated with survival outcomes. The median number of prior lines of therapy was 2 in each of the CLL-CI groups for R/R ibrutinib-treated patients (p=0.175).

Within the ibrutinib cohort, baseline cardiac comorbidities and hypertension were more frequent in intermediate and high risk CLL-CI groups. Cardiac comorbidities of any grade occurred in 15.7% of low risk, 33.8% of intermediate risk, and 44.4% of high risk CLL-CI patients (p<0.001). Severe cardiac comorbidities at the time of starting ibrutinib were recorded in 4.5%, 12.7%, and 12.7% of patient subsets, correspondingly (p=0.032). The prevalence of hypertension at the time of initiating ibrutinib also increased along with CLL-CI, with any grade (severe) hypertension rising from 35.8% (13.4%) to 59.2% (21.1%) to 71.4% (39.7%) among the low, intermediate, and high risk subsets (p<0.001).When computing correlation coefficients among pairs of CIRS variables, we found that vascular

and endocrine comorbidities were significantly correlated with both cardiac disease and hypertension in ibrutinib-treated patients (Spearman ρ = 0.15 to 0.27; Supplemental Table 3). However, had the CLL-CI score included cardiac and hypertension CIRS categories either (i) instead of the endocrine and vascular categories or (ii) in addition to the 3 CIRS variables chosen using RSF, the EFS concordance probability (computed from a Cox model containing known clinical predictors and a categorical or continuous comorbidity measure) for ibrutinib-treated patients would have decreased from 0.67 to 0.66 in each scenario (25). Thus, in the derivation set context, a comorbidity score would not be improved by including cardiac dysfunction and hypertension and would increase the risk of overfitting since cardiac and hypertension did not consistently appear as RSF top-ranked variables across the 100 random sub-samples of this dataset.

CLL-CI correlates with outcomes in a validation CLL patient cohort

We next evaluated the prognostic value of CLL-CI in an independent single-institution patient dataset (N=167). Compared with the derivation set, patients in the validation cohort were younger (median 64 years, range 36–88) and more likely to be analyzed while receiving frontline therapy (89% of patients; Table 1). The proportion of patients with ECOG ≥ 2 (4%, with 3% missing), aberrant *TP53* (22%), and treated with BTKi (50%) or with CIT (41%) was similar to the derivation set. Applying the CLL-CI score to this independent set of patients, 51% had low risk, 28% had intermediate risk, and 22% had high risk comorbidities. Median follow-up was 28 months (IQR 16–48, range 1–125) with 16 observed deaths and 37% of patients experiencing an EFS event. Patients were also treated with acalabrutinib (n=5) and venetoclax. In this cohort, 16 patients (20%) discontinued ibrutinib: 8 due to adverse events, 5 due to disease progression, and 3 patients died (Supplemental Table 4). Although 13 of these patients (81%) had CLL-CI >0 at the time of ibrutinib initiation, none were found to have contraindications for the use of ibrutinib.

The median EFS was 81 months (95% CI: 57-NA) in low risk, 40 months (95% CI: 19-NA) in intermediate risk, and 23 months (95% CI: 12–64) in high risk patients (log-rank p<0.001; Fig. 3A). As in the derivation dataset, upon adjusting for known prognostic factors, CLL-CI was significantly associated with EFS in the full sample (Fig. 3B) and within distinct clinical subgroups, including among patients treated with CIT or with BTKi (Supplemental Fig. 3, Supplemental Table 5). Estimated OS rate at 2 years was 96.8% in low risk, 91.7% in intermediate risk, and 88.2% in high risk CLL-CI (Fig. 3C). Upon adjusting for known clinical predictors, CLL-CI remained significantly associated with OS (Fig. 3D, Supplemental Table 6). Thus, CLL-CI retained its prognostic significance in an independent patient dataset.

Discussion

Prognostic models in CLL have been developed to predict outcomes in early stage disease as well as following treatment with CIT and targeted agents (29–31). However, none include an objective measure of comorbidity. This is likely due to the complexity of available clinical tools which measure comorbidities. CIRS is a comprehensive comorbidity scale adopted from the geriatric literature that correlates with survival in CLL but is time-intensive to

clinically implement. Compared to CIRS, our newly developed CLL-CI score is easy to apply to clinical practice, developed specifically for CLL patients, and, despite its simplicity, still able to identify a population of CLL patients with shorter survival. Thus, the CLL-CI fills a key clinical need by providing a user-friendly tool which can identify patients at risk for poor outcomes. The CLL-CI could also be an important research tool by allowing the inclusion of comorbidities into CLL prognostic models and by identifying comorbid patients for clinical trials, which remains an unmet medical need.

In this study, we deploy random survival forests – a machine learning technique comprising an ensemble of decision trees – to determine the most promising CIRS comorbidities in terms of predicting EFS in the presence of known prognostic factors (20,32). RSF was chosen for its ability to accommodate non-linear effects and complex interactions while identifying the most predictive comorbidities and optimal split points. Machine learning techniques have been used to identify CLL patients at risk for infection (33), and were recently employed to construct a risk score for predicting outcomes in CLL patients treated with ibrutinib (34). However, machine learning tools have not been used, to the best of our knowledge, to investigate comorbidities. Variable selection via RSF modeling was accomplished by identifying CIRS organ classes with the greatest impact on EFS according to tree structure (quantified by minimal depth [MD]) and out-of-sample prediction error rate (quantified by variable importance [VI]). By considering MD and VI rankings as well as the most frequent RSF split points (with these splits maximizing EFS differences), we sought to determine the most prognostic comorbidities in a diverse cohort of CLL patients. While VI and MD from RSF models have been presented in the context of variable selection (35,36), our application of these metrics is novel since they were used to identify ordinal-scale clinical variables most likely to predict outcomes in hematologic malignancies.

Using this innovative approach, we identified vascular, endocrine, and upper gastrointestinal CIRS organ system categories as the most predictive of EFS in patients with CLL. In our RSF models applied to random sub-samples of the derivation set, each of these three categories was in the MD-based top 3 CIRS variables 7 times more often than the next highest categories (renal and cardiac). In evaluating all RSF tree nodes to determine the most common split point for each of these 4-level ordinal CIRS variables and assigning 1 point for CIRS values above the split point (i.e. values representing a higher degree of organ dysfunction), the CLL-CI score was constructed as the sum of these points. The highest two values in this summary score were consolidated to avoid unstable estimates from small groups, resulting in 3 categories for CLL-CI: low risk (score = 0), intermediate risk (score = 1), and high risk (score = 2/3). This 3-category score is easy to clinically apply and interpret as a prognostic risk assessment tool.

Compared to CIRS, the CLL-CI has the distinct advantage of a simpler scoring system. Despite that, CLL-CI independently correlated with survival in both derivation and validation cohorts, a notable strength of this study. The CLL-CI is computed from just three organ system categories, compared to 14 for CIRS. Confirming previous findings, CIRS ≥7, a validated comorbidity threshold which has been used in many CLL clinical trials (3,5,27,37), was highly associated with EFS (HR=2.10, $p<0.001$). However, the difference in EFS between high risk and low risk CLL-CI patients was even greater in magnitude

(HR=2.64, p<0.001 for the derivation set; HR=5.09, p<0.001 for the validation set). Like CIRS, the CLL-CI was independently associated with shorter EFS in clinically-relevant subgroups (i.e. treated with CIT or BTKi, in frontline or R/R setting). There was also an independent correlation between CLL-CI and risk of any-cause death among all CLL patients in both of our datasets. In subgroup analyses of OS, CLL-CI was statistically significant in the frontline setting (overall p<0.001 in the derivation set, high risk vs. low risk p=0.049 in the validation set), and there were trends in the other subgroups towards shortened survival in higher levels of CLL-CI. These CLL-CI effects may attain significance with longer follow-up since only 19% and 10% of our derivation set and validation set patients had an OS event, respectively.

The most frequently involved organ systems by CIRS category – hypertension, musculoskeletal, and respiratory – were not top predictors of EFS in our ensemble survival tree approach. Notably, hypertension is a common adverse event with ibrutinib and increases the risks of major complications (38). Although the prevalence of severe cardiac comorbidities was 9.4% among ibrutinib-treated patients and there is a known association between BTKi's and increased incidence of atrial fibrillation (up to 16% in some trials) (39), the cardiac CIRS category was also not a top predictor according to our RSF analysis. Given that the majority of patients (59%) in our derivation dataset were treated with ibrutinib, it was unexpected that cardiac comorbidities and hypertension did not rank higher in RSF models. And yet, these comorbidity types were more frequently encountered in patients with higher CLL-CI. Clinically, there is considerable overlap between the distinct CIRS categories. For example, the metabolic syndrome would include vascular, endocrine, and hypertension CIRS categories. Furthermore, multiple studies have demonstrated that hypertension and cardiac disease are more prevalent in patients with vascular disease (e.g. carotid stenosis or peripheral vascular disease) and endocrine disorders (e.g. obesity or diabetes mellitus) (40,41). We also found a significant correlation between these comorbid conditions. However, in our study, neither cardiac conditions nor hypertension improved the discriminative power of CLL-CI.

A strength of this analysis is the relatively representative nature of the patients included in the development of CLL-CI. In the derivation dataset, median age was 67 years, 50% of patients harbored at least one severe comorbidity, the majority received ibrutinib, and 20% had del(17p)/*TP53* mutation. Accurate prognostication is inherently of value to patients and providers and our score does assist in that regard. Our data suggest that comorbidities may have a larger impact on outcomes in the frontline setting which leads us to hypothesize that comorbid patients may achieve a greater benefit from intensive frontline therapy (e.g. combination BTKi, anti-CD20, and venetoclax rather than sequential therapy) compared to non-comorbid patients.

An important limitation of our study is that the data came from retrospective chart review and analyses are thus confined to available, reported information. We did not record the specific events that led to discontinuation of ibrutinib in the derivation cohort. Thus, it is possible that patients who discontinued ibrutinib may have had relative contraindications to its use. This is a limitation of our analysis. It is important to note, however, that adverse events and progressive disease were the most common reasons for ibrutinib

discontinuation in the validation cohort and a detailed review of patient records did not reveal contraindications for using ibrutinib. While there is some subjectivity in CIRS scoring, our previous work has demonstrated a strong correlation between graders (10). Additionally, while we include an external validation cohort, the relatively small size (N=167) and duration of follow-up (median, 28 months) may limit its generalizability. Another limitation of the CLL-CI is that it does not help select the optimal treatment for comorbid patients as increased CLL-CI risk was found to be associated with shortened survival in all evaluated therapies. The simplicity of the CLL-CI is both an advantage and a potential limitation and providers must remain cognizant of each individual patient's complete medical history.

Ours is the largest cohort of ibrutinib-treated patients to be assessed for the effect of comorbidities in a systematic manner. We found that both high CIRS (consistent with our previous work) and higher risk CLL-CI correlate with shortened survival and inferior tolerance to ibrutinib (11). It remains to be seen whether these findings are applicable to other novel therapies, such as BCL2 inhibitor venetoclax and BTKi acalabrutinib (7,42). While our validation dataset included patients treated with these agents, small numbers in these groups precluded subgroup analyses. Nevertheless, the fact that CLL-CI is based on a heterogeneous patient cohort exposed to a variety of treatments, and that it retained its prognostic value in a validation dataset that included additional novel agents, increases the likelihood of its applicability to all CLL. With this in mind, our current work focuses on developing comorbidity-inclusive models which will help inform physician's choice between novel therapies.

In summary, in our study populations, comorbidities identify a subset of CLL patients with shorter survival. We identified the three most EFS-predictive CIRS organ classes and constructed a new simplified measure of comorbidity, the CLL-CI, that independently associated with survival in CLL patients, including those treated with BTKi. Importantly, our key findings were validated in an independent external cohort. The impact of this research could have broad clinical application to clarify prognosis for CLL patients and may be applicable to other lymphoid malignancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interests:

A.V.D. received research funding from AstraZeneca, Takeda Oncology, Genentech, Bayer Oncology, SecuraBio and Bristol-Myers Squibb, and consulted for Abbvie, Beigene, Bayer Oncology, AstraZeneca, Karyopharm, Genentech, Pharmacyclics, and TG Therapeutics.

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Translational relevance

Comorbidities are predictive of poor tolerance of chemo-immunotherapy in patients with CLL and remain a negative prognostic marker in the era of targeted therapies. General comorbidity indices adopted from geriatric medicine, such as the cumulative illness rating scale (CIRS), are predictive of survival but are difficult to calculate and may not accurately estimate the relevance of specific conditions in CLL. Using a machine learning technique, we identified comorbidities most predictive of outcomes in a multicenter CLL patient cohort and developed a CLL-specific comorbidity index (CLL-CI) which was then validated in an independent dataset. CLL-CI is easy to score and independently correlates with survival in both chemotherapy and novel therapy settings in CLL. CLL-CI can improve prognostication when counseling patients, facilitate the inclusion of comorbidities into CLL prognostic models and help incorporate comorbidity scoring into clinical trials.

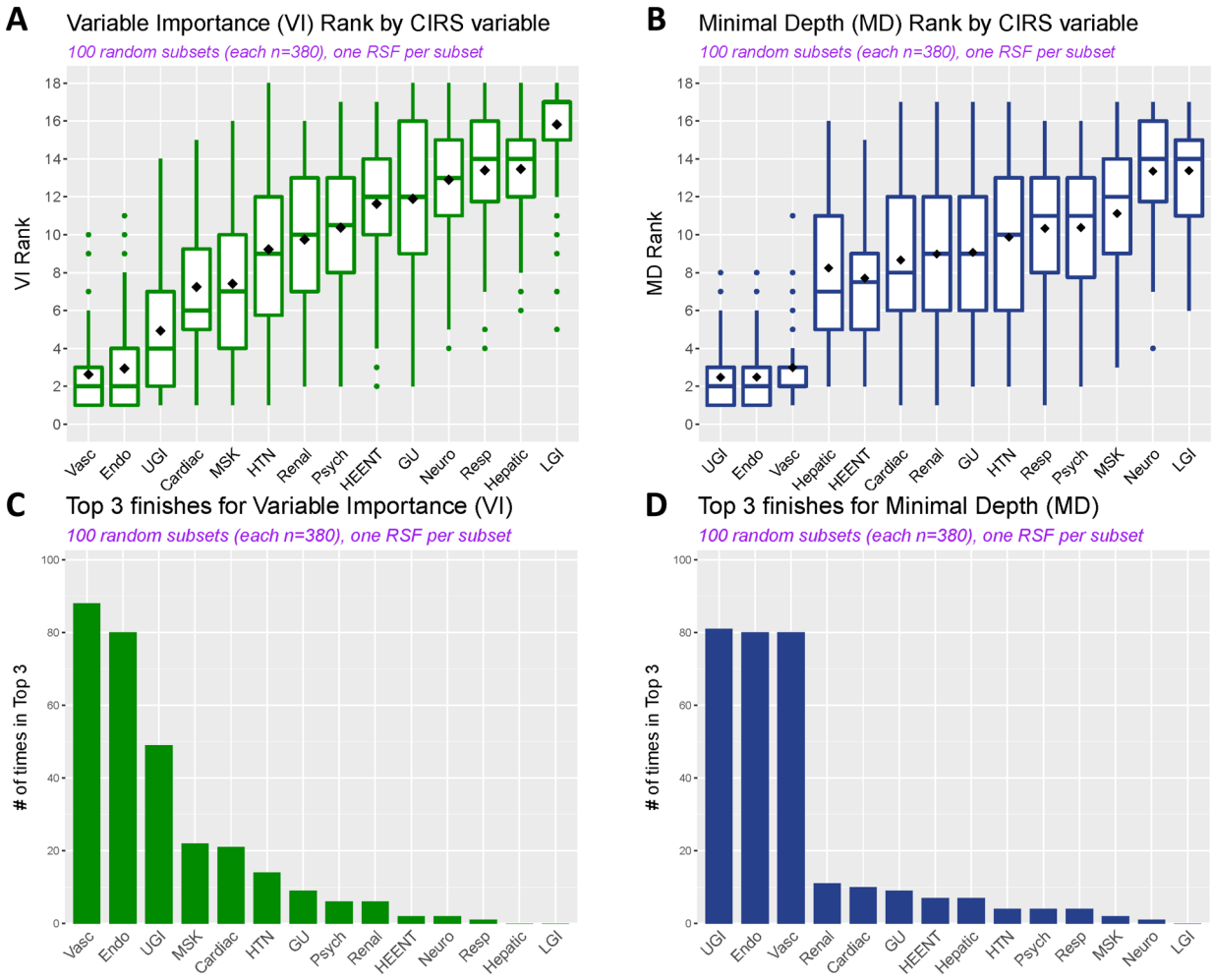

Figure 1. Construction of the CLL-CI index.

(A, B) Variable ranks by VI and MD, as computed from RSF modeling of EFS, for 100 random sub-samples (each with n=380) of the derivation dataset. *(C, D)* Frequency of top 3 rankings (among all CIRS classes) according to VI or MD for the 100 random sub-samples. CIRS class abbreviations: ‘Endo’ = Endocrine / metabolic; ‘GU’ = Genitourinary (non-renal); ‘HEENT’ = Head, Eye, Ear, Nose, and Throat; ‘HTN’ = Hypertension; ‘LGI’ = Lower gastrointestinal; ‘MSK’ = Musculoskeletal / integumentary; ‘Neuro’ = Neurological; ‘Psych’ = Psychiatric / behavioral; ‘Resp’ = Respiratory; ‘UGI’ = Upper gastrointestinal; ‘Vasc’ = Vascular / hematological

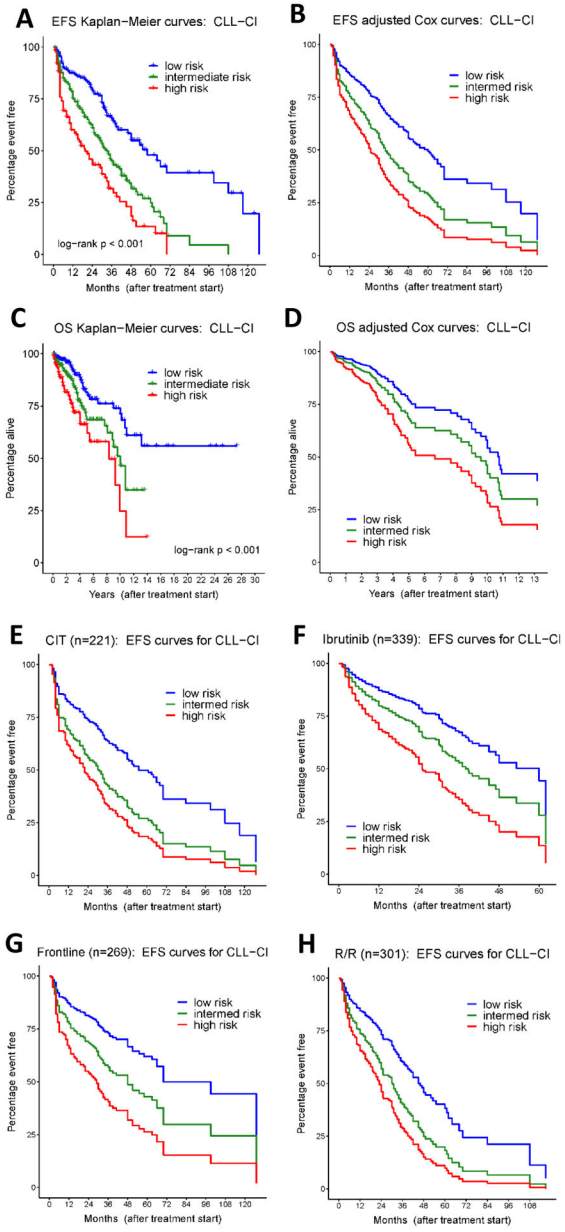

Figure 2. CLL-CI predicts survival in patients with CLL (derivation dataset, N=570).

(A, C) Kaplan-Meier curves by CLL-CI category and log-rank test p-value for EFS and OS when evaluating all patients. *(B, D)* Multivariable Cox model adjusted (for 4 prognostic factors) curves by CLL-CI category for EFS and OS on all patients. *(E-H)* Cox model adjusted EFS curves by CLL-CI category among patients receiving CIT (E), ibrutinib (F), treated in the frontline setting (G) and in the R/R setting (H).

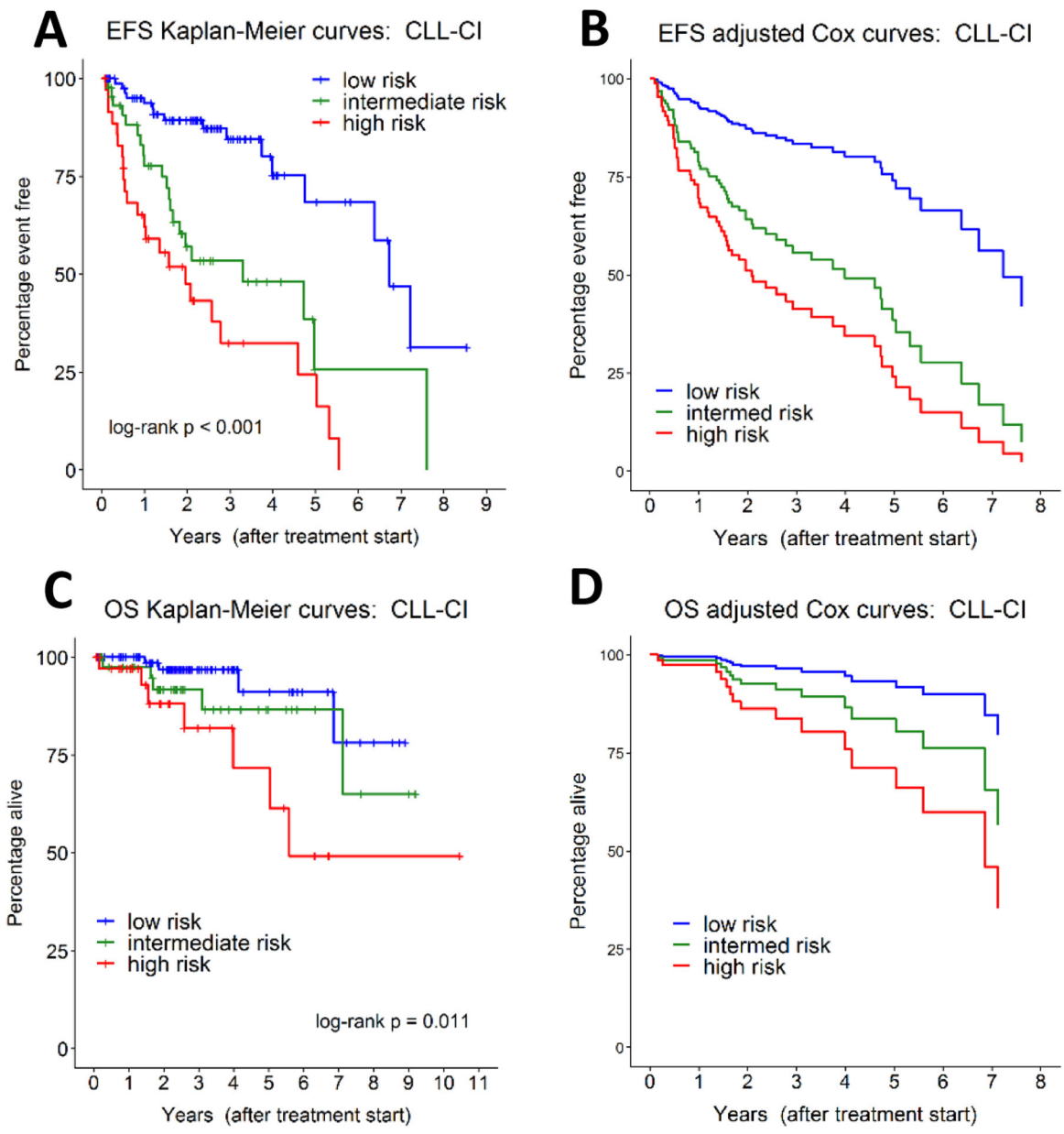

Figure 3. CLL-CI predicts survival in patients with CLL (validation dataset, N=167).

(A, C) Kaplan-Meier curves by CLL-CI category and log-rank test p-value for EFS and OS when evaluating all patients in the validation set. *(B, D)* Multivariable Cox model adjusted (for 4 prognostic factors) curves by CLL-CI category for EFS and OS on all patients.

Table 1:

Baseline patient characteristics for derivation and validation datasets.

	Dataset (sample size)	
Patient characteristic	**Derivation (N=570)**	**Validation (N=167)**
Age		
Median (range)	67 (31–90)	64 (36–88)
≥65 years	352 (62%)	78 (47%)
≥80 years	66 (12%)	10 (6%)
ECOG		
0	276 (48%)	71 (43%)
1	207 (36%)	85 (51%)
≥2	36 (6%)	6 (4%)
Unknown	51 (9%)	5 (3%)
Cytogenetics		
Del(17p) / *TP53* mutation	114 (20%)	36 (22%)
Del(11q)	111 (19%)	29 (17%)
Treatment setting		
Frontline (*de novo*)	269 (47%)	148 (89%)
R/R	301 (53%)	19 (11%)
Treatment type		
Fludarabine ± anti-CD20	104 (18%)	20 (12%)
Bendamustine ± anti-CD20	35 (6%)	23 (14%)
Chlorambucil ± anti-CD20	33 (6%)	5 (3%)
BTKi * ± anti-CD20	339 (59%)	84 (50%)
Venetoclax ± anti-CD20	0 (0%)	9 (5%)
Other	59 (10%)	26 (16%)
CIRS		
Median (range)	7 (0–29)	N/A
CIRS ≥7	302 (53%)	N/A
CIRS 3+	284 (50%)	N/A
CLL-CI variables		
Vascular (CIRS > 0)	182 (32%)	44 (26%)
Upper GI (CIRS > 1)	182 (32%)	29 (17%)
Endocrine (CIRS > 1)	176 (31%)	50 (30%)

* BTKi included ibrutinib in the derivation dataset and ibrutinib or acalabrutinib in the validation dataset

Table 2.

Medical conditions that contribute to the CLL-CI score.

Category	Example medical conditions	Score
Vascular (any CIRS grade comorbidity)	Venous insufficiency/lymphedema, carotid stenosis, DVT or PE, symptomatic atherosclerosis (e.g. claudications, TIA, angina) or requiring surgical/endovascular intervention, daily antiplatelet use, aortic stenosis	1 point
Upper GI (moderate-to-severe, CIRS score ≥2)	Daily PPI, documented PUD, acute or chronic pancreatitis, melena, prior gastric cancer, history perforated ulcer	1 point
Endocrine (moderate-to-severe, CIRS score ≥2)	Diabetes treated with oral agents or insulin, hyperthyroidism, obesity (BMI >35), adrenal insufficiency, thyroid, breast or adrenal malignancy	1 point

Sum of points is used to calculate CLL-CI. CLL-CI score of 0 is low risk, 1 is intermediate risk, and 2–3 is high risk.

Abbreviations: DVT - deep vein thrombosis; PE - pulmonary embolism; TIA - transient ischemic attack; PPI - proton pump inhibitor; PUD - peptic ulcer disease; BMI - body mass index.

Table 3.

CLL-CI group effects on EFS and OS from multivariable Cox models (derivation dataset).

Population (n)	CLL-CI pairwise comps.	EFS HR (95% CI)	EFS c-stat*	OS HR (95% CI)
All patients (570)	Intermediate vs low	1.83 (1.35 – 2.47) p<0.001	0.65	1.51 (0.94 – 2.43) p=0.091
	High vs intermediate	1.45 (1.07 – 1.95) p=0.015		1.61 (1.00 – 2.59) p=0.048
	High vs low	**2.64 (1.86 – 3.75) p<0.001**		**2.43 (1.41 – 4.21) p=0.001**
Ibrutinib (339)	Intermediate vs low	1.65 (1.07 – 2.54) p=0.024	0.67	1.59 (0.79 – 3.18) p=0.193
	High vs intermediate	1.70 (1.09 – 2.63) p=0.018		1.47 (0.74 – 2.91) p=0.266
	High vs low	**2.79 (1.68 – 4.65) p<0.001**		**2.34 (1.04 – 5.23) p=0.039**
CIT (221)	Intermediate vs low	1.93 (1.25 – 2.97) p=0.003	0.64	1.63 (0.83 – 3.23) p=0.159
	High vs intermediate	1.31 (0.87 – 1.98) p=0.197		1.74 (0.89 – 3.42) p=0.105
	High vs low	**2.53 (1.55 – 4.14) p<0.001**		**2.85 (1.31 – 6.18) p=0.008**
Frontline (269)	Intermediate vs low	1.83 (1.13 – 2.97) p=0.014	0.67	1.61 (0.76 – 3.41) p=0.217
	High vs intermediate	1.65 (1.02 – 2.68) p=0.040		2.71 (1.28 – 5.74) p=0.009
	High vs low	**3.03 (1.80 – 5.09) p<0.001**		**4.35 (2.01 – 9.45) p<0.001**
R/R (301)	Intermediate vs low	1.82 (1.23 – 2.67) p=0.002	0.63	1.35 (0.70 – 2.61) p=0.366
	High vs intermediate	1.39 (0.94 – 2.04) p=0.099		1.35 (0.71 – 2.58) p=0.362
	High vs low	**2.52 (1.58 – 4.02) p<0.001**		**1.83 (0.84 – 3.97) p=0.128**

CLL-CI hazard ratios (HR's) and p-values reflect statistical adjustment for age, treatment setting, type of therapy, and *TP53* aberrancy. The second group listed in a given row is the reference group for interpreting HR's.

*Gonen-Heller concordance probability estimate