


LETTER TO THE EDITOR

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Clinical characteristics and outcome of SARS-CoV-2 infection in admitted patients with chronic lymphocytic leukemia from a single European country

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Letter to the editor

Spain has been one the most affected countries by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) pandemic [1, 2]. Patients with chronic lymphocytic leukemia (CLL) could be at risk of more severe COVID-19 clinical forms [3] since they often carry immune perturbations aggravated by treatments used for the disease itself [4]. Two major series on patients with COVID-19 and CLL encompassing different countries and health systems reported heterogeneous factors related to the outcome [5, 6]. Herein, we are presenting the largest series of CLL patients with proved COVID-19 from a single country and Health system.

We identified 165 patients with CLL and COVID-19 across 40 Spanish centers (Additional file 1: Table S1 and S2) between March 1, 2020 and May 31, 2020. In summary, at the time of infection median age was 73 years, 27% were younger than 65, and 40% had comorbidities (CIRS \geq 6). Eighty-five patients (52%) were in watch & wait (W&W), 34 (21%) had been previously treated, whereas 46 patients (28%) were currently on CLL treatment, mainly with BTK inhibitors (BTKi) (n=34) and venetoclax (n=7). Increased CRP (>0.3 mg/dL) was detected in 27.8%, increased D-dimer (>500 mg/mL) in 70%, ferritin >400 mg/mL in 74%, and elevated IL-6 in 88% of patients in whom it was assessed. Among these inflammatory parameters, ferritin and D-dimer were significantly lower in patients receiving BTKi at the time of COVID-19 compared to the others (Additional file 1: Fig. S1). 92% of the patients required hospital admission, with 31% requiring intensive management.

Regarding survival, 45 deaths (27%) were observed, all of them due to SARS-CoV-2 infection. The case fatality

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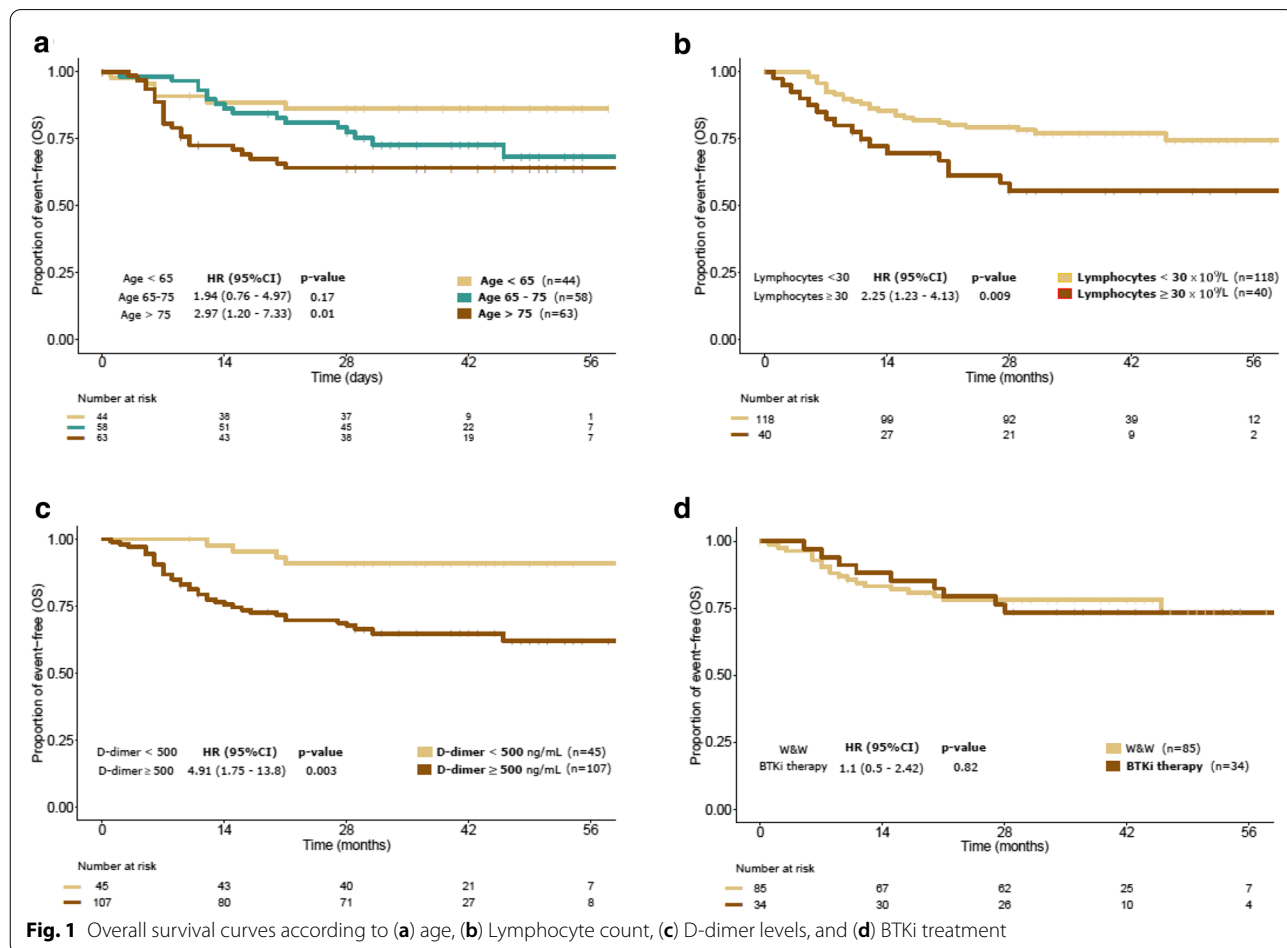
rate (CFR) for admitted patients was 33.6% and the OS estimates of the entire cohort at 28 days was 74.1%. In the univariate analysis, age, CIRS ≥ 6 , Binet stage B-C, hemoglobin < 10 g/dL, lymphocytosis ($\geq 30 \times 10^9/L$), CRP, and D-dimer levels were associated with OS. At the multivariate analysis, age (HR = 1.36, [95% CI 1–1.86]), lymphocytosis (HR = 1.96, [95% CI 1.05–3.63]), and D-dimer (HR = 4.35, [95% CI 1.53–12.3]) maintained its independent statistical significance (Fig. 1 & Additional file 1: Table S3). Patients on W&W presented similar OS than patients receiving an active CLL-directed therapy. Notably, treatment with BTKi (n = 34) did not influence mortality of the infection in comparison with patients on W&W (HR: 1.1 [CI 95% 0.5–2.42]; Fig. 1d).

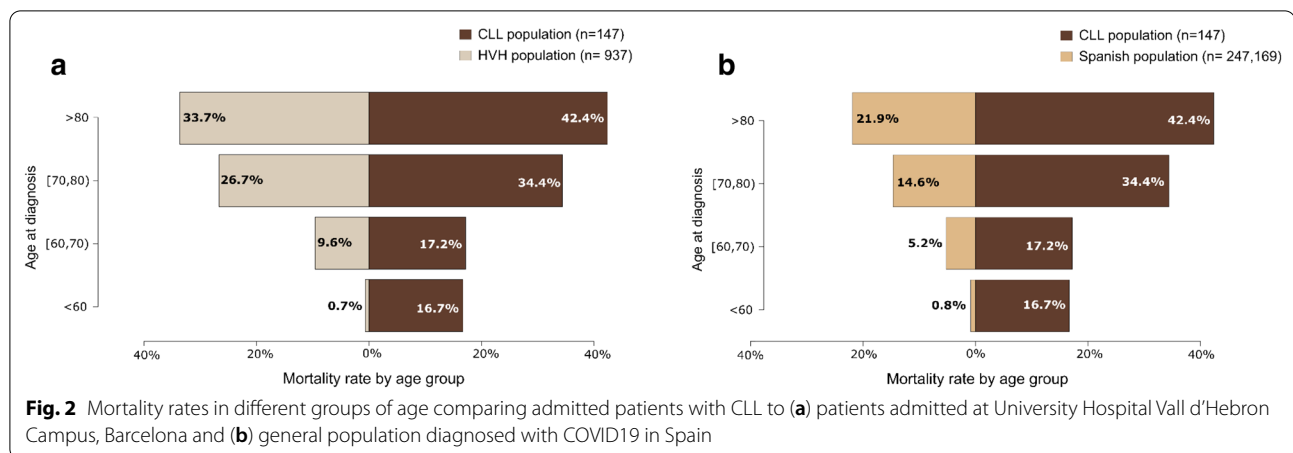
Mortality rate by segments of age was contrasted with 937 patients admitted for COVID-19 at University Hospital Vall d’Hebron, excluding patients with hematologic malignancies, solid tumors, or with other causes of immunosuppression. Overall, mortality rates were higher in CLL patients (adjusted OR = 1.74 [95% CI 1.14–2.65], p = 0.01). The major difference between both cohorts was observed in the higher mortality for CLL

patients < 60 years (16.7% vs 0.7%, p < 0.001). Of note, three out of the four young CLL patients that died were untreated and lack comorbidities, suggesting a negative effect of CLL in those patients. Finally, mortality was significantly higher compared to the mortality rates by age reported by the Spanish Ministry of Health up to May 2020 (adjusted OR = 3.91 [95% CI 2.70–5.66], p < 0.001) (Fig. 2 and Additional file 1: Table S4).

The inferior survival observed in patients with CLL and COVID-19 in our series seems to be similar to the data reported in other series of patients with hematologic malignancies, pointing to a patient population more vulnerable to COVID-19 infection [7].

In summary, in our series mortality rate was 27%, with a CFR for admitted patients of 33.6%, resembling the ones reported by Mato et al. [5] and by the ERIC/CLL Campus series [6]. In contrast to the observations reported by the ERIC/CLL Campus series, and in agreement with Mato et al. [5], age and comorbidities were strongly related to mortality. Importantly, and as opposed to the two former mentioned series [5, 6], lymphocytosis was associated with OS, suggesting that a more active





CLL disease at the time of infection could increase the vulnerability to COVID-19. The inflammatory parameters analyzed in our series correlated with COVID-19 outcome. Thus, increased CRP and D-dimer predicted for a shorter survival, the latter maintaining its adverse prognostic impact in the multivariate analysis. Finally, in our series and in agreement with Mato et al. [5] patients receiving BTKi at the time of COVID-19 presented similar outcome as patients never treated and, accordingly exhibit lower levels of ferritin and D-dimer, which could be in part explained by the suggested protective role of BTKi against SARS-CoV-2 infection severity due to its immune-modulator effect [8–10].

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s40164-020-00195-x>.

Additional file 1: Table S1. Patient and CLL features at the time of COVID-19 infection (n = 165). **Table S2.** COVID-19 manifestations, management, and outcomes. **Table S3.** Univariate and multivariate OS analysis of baseline characteristics. **Table S4.** Characteristics of patients infected by SARS-CoV-2 i) treated at University Hospital Vall d'Hebron and ii) overall Spanish population. **Figure S1.** Levels of inflammatory parameters according to treatment with BTKi. (* indicates $p < 0.05$).

Authors' contributions

All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interest.

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