Changes in cardiac parameters during venetoclax treatment

Venetoclax is one of the mainstays of therapy for chronic lymphocytic leukemia (CLL) and several other hematologic neoplasms.[1] It is applied either as monotherapy or combined with anti-CD20 antibodies, inhibitors of the Bruton´s tyrosine kinase (BTK),[2] epigentic modifiers, immunochemotherapy[3] or hypomethylating drugs.[4] The mechanism of action of venetoclax is based on inhibition of the anti-apoptotic protein BCL-2 with a subsequent shift towards apoptosis.[5] BCL-2 is involved in cytochrome c release from mitochondria and expressed in many tissues including the heart.[6]

Cardiac toxicity of targeted drugs for lymphomas is generally ascribed to BTK inhibitors, however, occasional cardiac events including cardiac arrests were reported in venetoclax-based studies.[1] Johnson *et. al*. reported cardiac events in 20% of patients with acute myeloid leukemia (AML) treated with a combination of venetoclax and hypomethylating agents.[7] Grewal and colleagues searched the Food and Drug Administration (FDA) Adverse Event Reporting System database for ibrutinib, acalabrutinib, venetoclax, and idelalisib. Surprisingly, the highest mortality associated with 6,074 cardiac events was found in patients receiving venetoclax (29.4%).[8] However, biomarkers for risk assessment are lacking. We therefore investigated serum markers of cardiac toxicity in relation to venetoclax dose and clinical course in patients receiving mono- or combination-therapy for various hematologic entities.

Fifty-five predominately male (N=35, 63.63%) and Caucasian (N=54, 98%) adults (>18 years) at the Department of Hematology at the Medical University of Vienna receiving venetoclax between 2016 and 2019 were included after informed consent (*Online Supplementary Table S1*). Diagnoses included CLL (N=32), acute myeloid leukemia (AML) (N=4), secondary AML (N=3), T-cell pro lymphocytic leukemia (T-PLL, N=5), diffuse large B-cell lymphoma (DLBCL, N=11). Follow-ups were collected until 2021.

The median age was 69.4 (range, 58.2-75.5) years. Venetoclax was given as third line of treatment in median and administered doses ranged from 10 mg to 1,200 mg (CLL up to 400 mg, AML 400 mg, T-PLL up to 1,200 mg, DLBCL up to 800 mg). Management of patients, including routine laboratory testing and treatment were not influenced by the study and performed at the discretion of the attending physician. Data was extracted from routine retrospectively. The study was approved by the local Ethics committee (EK 1568/2018; 2015-1205).

Normal ranges for troponin T (TnT, electrochemiluminescence immunoassay) were 0-14 ng/L and for creatinine 0.7-1.2 mg/dL for men and 0.5-0.9 mg/dL for women. Polymorphisms of CYP3A4, CYP3A5 and UGT1A1 were examined routinely for potential pharmacogenetic implications.

Venetoclax serum levels were determined by mass spectrometry coupled to high-performance liquid chromatography using a Nexera system (Shimadzu, Scientific Instrument Inc., Columbia, MD, USA) and a 6500 Qtrap system (AB Sciex, Concord, ON, Canada) with Analyst software version 1.6.2 (Sciex).

Variables are presented as absolute numbers, relative frequencies and medians with interquartile ranges (IQR). Firstly, the correlation between the dose and the resulting serum level of venetoclax was analyzed accounting for interpersonal variations as random effects. Laboratory markers were assessed with Wilcoxon signed-rank test for dependent variables and mixed-effects regression models were used to analyze dose dependency and compensating for creatinine levels. Genetic polymorphisms and rates of cardiovascular events were analyzed descriptively. The statistical analysis was conducted with R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). *P* values below 0.05 were considered statistically significant.

Initially we aimed to evaluate creatine kinase (CK), CK-MB, NT pro brain natriuretic peptide (NT-proBNP), myoglobin and TnT levels before and during venetoclax therapy. It was impossible to thoroughly examine the effect of CK, CK-MB, NT-proBNP and myoglobin due to limited data quality in terms of temporal inconsistency and no significant increases were observed in the sparse data available. However, TnT proved to be a sensitive parameter and was available in 51 patients. The upper normal limit was crossed at least once by 80.4% of patients during venetoclax therapy in comparison to 43.1% before (*P*=0.003). In median the upper normal limit was crossed once before and seven times during venetoclax therapy (*P*<0.001). The median baseline TnT level was 13 (IQR, 8.75-25.25) ng/L and 25 (IQR, 14-35.25) ng/L during venetoclax therapy (*P*=0.001; Figure 1). Median peak TnT level during therapy was 36 (IQR, 19-53) ng/L. A decline in TnT levels after the end of venetoclax therapy was observed (particularly in CLL and DLBCL patients) reaching nearly baseline levels (14.3 [IQR, 7.85-28.6] ng/L; *P*=0.045).

Venetoclax serum levels with correlating doses were available in 31 patients at 138 time points ranging up to 5,960 ng/mL. Regression analysis estimated an increase of 0.77 ng/mL per mg venetoclax (*P*<0.001; Figure 2A). Data from 20 CLL patients receiving stepwise escalating doses of venetoclax also showed a dose-dependent increase (Figure 2B). Subsequently, the administered dose was used as surrogate marker in further analysis.

Simultaneous data on venetoclax dose, TnT and creati-

nine was available in 37 patients (25 CLL patients) at 409 points of time (*Online Supplementary Figure S1*). Regression analysis estimated an increase of 0.025 ng/L TnT per mg venetoclax (P=0.001) as well as 51.36 ng/L per mg/dL creatinine (P<0.001) remaining highly significant after adjusting for diagnoses. This adjustment revealed significantly higher TnT levels in AML patients (other diagnoses did not reach statistical significance.)

No clear influence of the polymorphic CYP3A4*22, CYP3A5*3 as well as UGT1A1*28 could be deduced from the present data.

Reported clinical events included dyspnea (N=12, 21.8%), extrasystoles (N=2, 3.6%), reduction in the ejection fraction (N=1, 1.8%), heart failure (N=1, 1.8%), myocardial infarction (N=1, 1.8%), circulatory collapse with TnT elevation (N=1, 1.8%) and disturbances of repolarization (N=1, 1.8%). None of these events resulted in death. Patients with cardiorespiratory events clustered in a higher TnT group (28.25 [IQR, 23.875-44.125] *vs*. 17.5 [IQR, 9.75,27.625]; P=0.004; Figure 3).

Most patients (N=45) did not receive venetoclax monotherapy but various combination therapies including obinutuzumab, rituximab, ibrutinib or azacitidin (*Online Supplementary Table S2*). While the increase in TnT was less marked in combination therapies, it remained dependent on venetoclax dose (P=0.002).

Venetoclax is generally not known for its considerable cardiac toxicity. However, cardiac events including sudden death occurred in clinical studies with venetoclax or combinations thereof.[2,7,8] Furthermore, a recent pharmacovigilant analysis of the FDA database found a surprisingly high rate of cardiac events in association with venetoclax.[8] Previous safety analyses revealed no association between exposure and adverse events.[9,10]

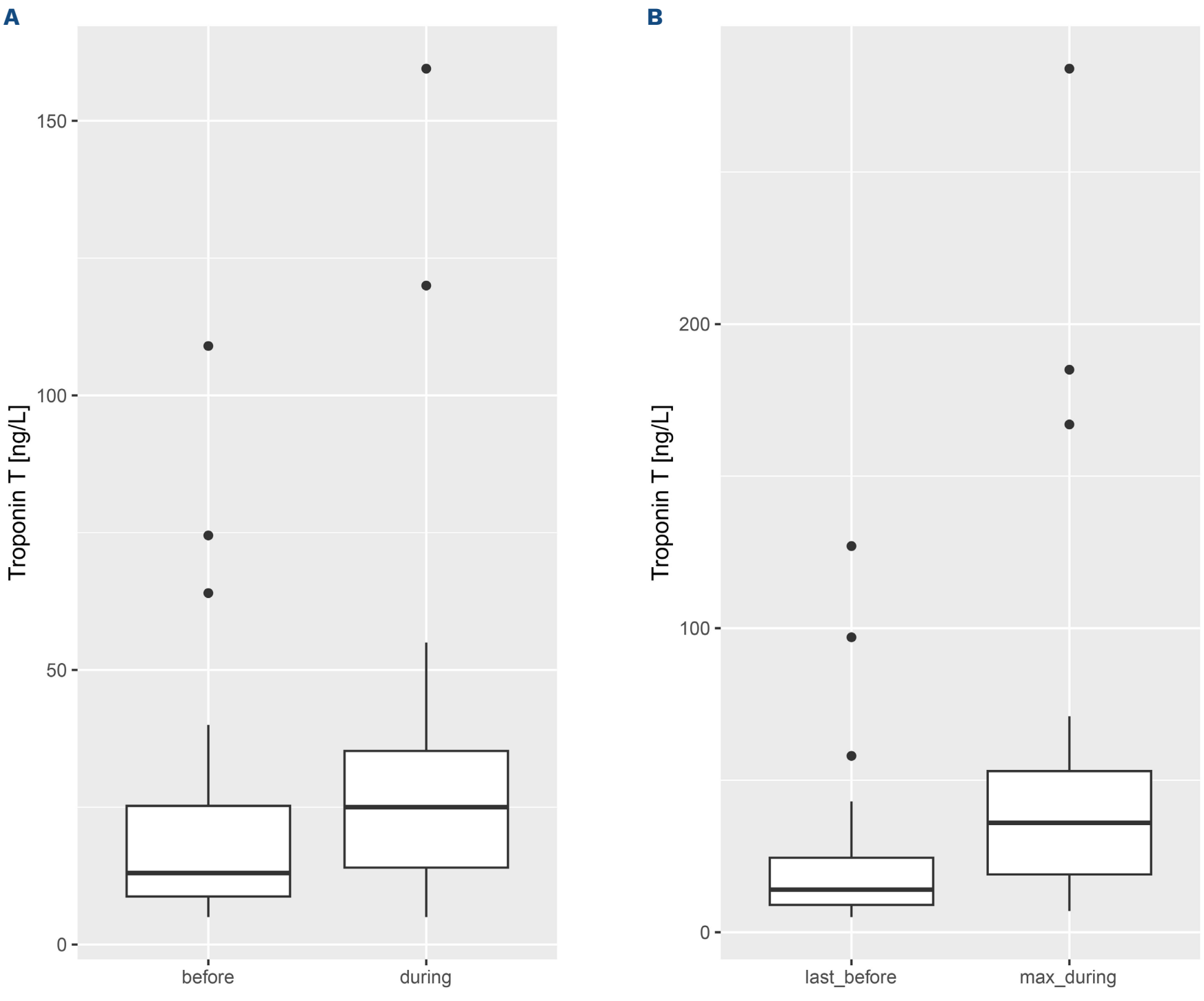

Figure 1. Comparison of troponin T levels before and during venetoclax therapy. (A) Increase of median troponin T (TnT) levels per patient before in comparison to during therapy. (B) Comparison of the last TnT level before initiation of therapy and maximum (max) level during therapy per patient.

TnT is known to be an indicator of myocardial damage[11,12] of distinct diagnostic importance in myocardial infarction but also plays a role in cardiomyopathy.[11] Furthermore, it may be useful for assessment of risk and prognosis regarding heart failure and cardiovascular disease. The association of venetoclax dose with TnT raises concerns regarding a certain degree of cardiac damage and/or a higher risk to develop such damage. Consistently, patients with clinical cardiopulmonary events showed higher TnT levels. Of note, we observed (non-significantly) higher TnT levels in males than in females in line with previous publications.[13] While *BCL-2* expression in healthy cardiomyocytes is low,[6] it may be induced under cardiac stress to prevent myocyte damage.[14] Thus, venetoclax probably does not induce cardiac events or damage under stable conditions, but could interfere with this process rendering patients more susceptible to cardiac damage as *BCL-2* expression increases.[14] This particularly applies for elderly patients, patients with combination treatments with cardiac effects (e.g., anthracyclines) or pre-existing cardiac comorbidities such as dilated cardiomyopathy with upregulated *BCL-2*. Effects in pulmonary artery smooth muscle cells[15] could be another reason for cardiorespiratory events by influencing pulmonary vascular remodeling.

We note that the population receiving venetoclax is generally older or affected by comorbidities such as patients with CLL receiving obinutuzumab combined with venetoclax according to the CLL-14 study. This is also true for patients with AML receiving venetoclax with azacytidine who are usually ineligible for aggressive treatment. Considerable cardiac toxicity was observed in this group.[7] We noted higher TnT levels in our small group of AML patients. In addition, the influence of azacytidine or concomitant treatment cannot be exactly quantified. The fact remains that this type of combination treatment seems to have a more pronounced effect regarding TnT.

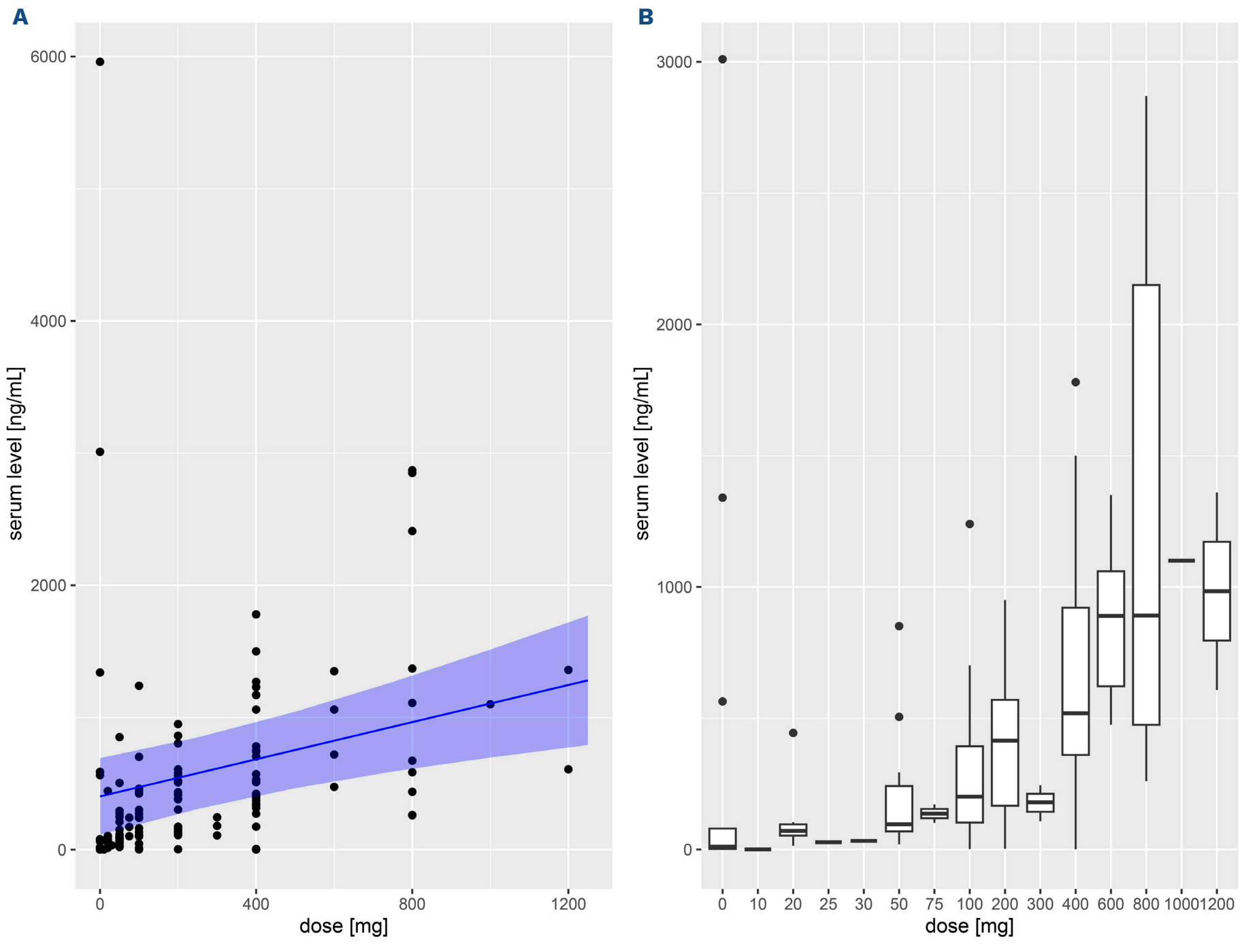

Figure 2. Overview of venetoclax serum levels and administered doses. (A) Serum levels and administered dose of venetoclax. (B) Increase of venetoclax serum levels during stepwise escalation therapy (ramp-up) in chronic lymphocytic leukemia (CLL) patients (N=20).

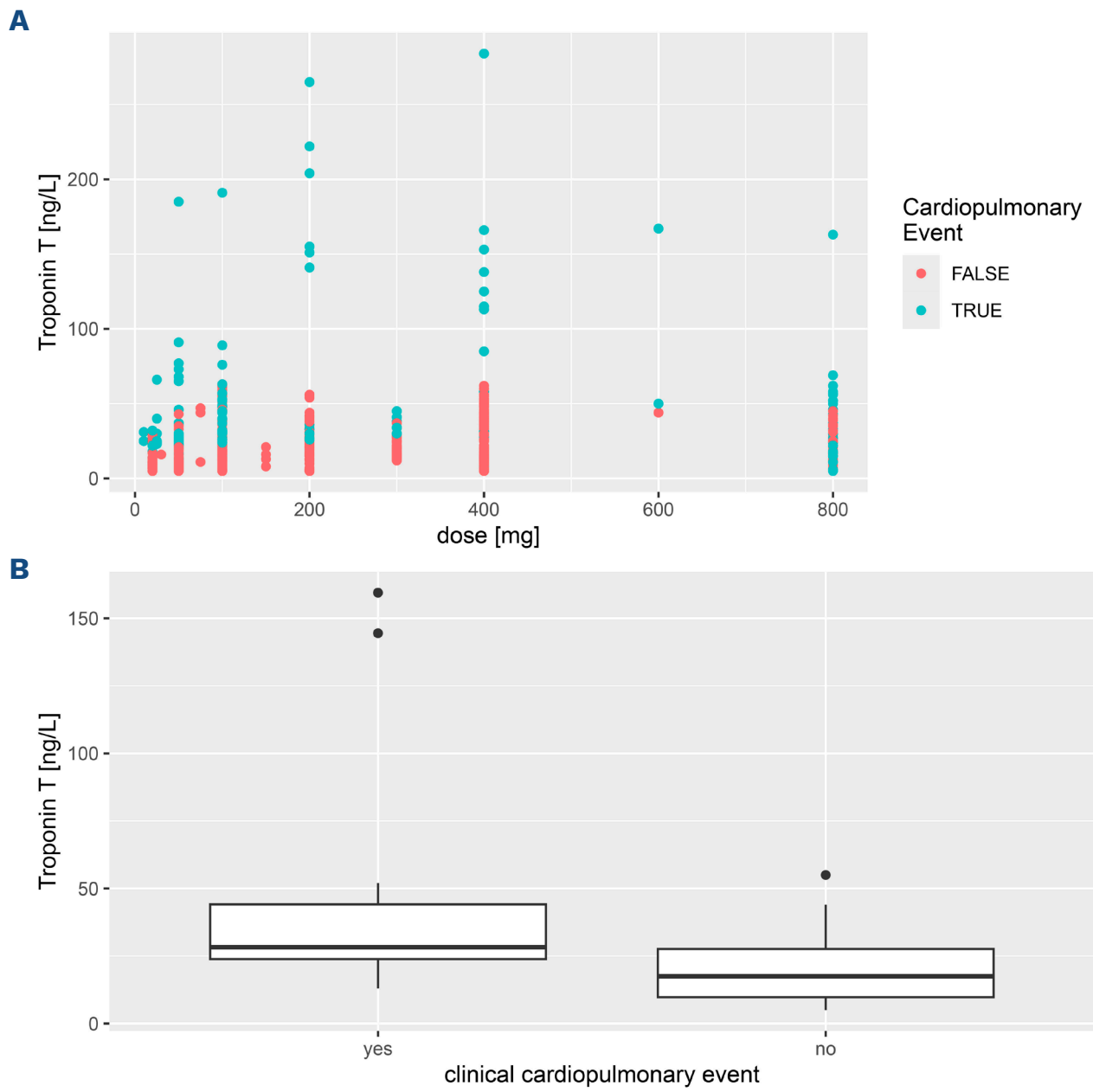

Figure 3. Overview of cardiopulmonary events in patients receiving venetoclax. (A) Association of troponin T (TnT) levels with venetoclax doses separated by occurrence of a clinical cardiopulmonary event. (B) Comparison of TnT levels between patients with and without a clinical cardiopulmonary event.

Since most of our patients received combinations of venetoclax with antibodies or other drugs, it is difficult to assess the influence of drug-drug interactions. Although effects (even single-agent effects) of other drugs cannot be excluded, the fact that TnT elevation was significant even with the venetoclax ramp-up in CLL suggests a clear influence of this drug. Further limitations arise primarily from the retrospective nature, and therefore the lack of routine assessments of cardiac function (e.g., transthoracic echocardiography, stress tests, invasive diagnostic procedures), and the low number of patients. Laboratory investigations were conducted based on physicians´ discretion potentially biased towards patients with elevated cardiac risk. Time of observation was limited possibly neglecting long-term cardiovascular side effects. Furthermore, assessment of venetoclax serum levels was limited due to poor availability of therapeutic drug monitoring for venetoclax. Regarding pharmacogenetics, the small divergence of genotypes limited the analysis drastically. While the clinical impact of elevated TnT during venetoclax remains unknown, it is important to keep the described effect in mind during routine follow up or in case of an acute event. Whether it may serve as a biomarker of an elevated cardiovascular risk in such patients must be explored in controlled clinical trials.

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Contributions

EP and UJ designed the study. PC, CS, RT, OF, ISK, WS, KG, MS, RS, KV, CG, PS and UJ contributed data. RB analyzed data. UJ and RB wrote the manuscript. All authors contributed to and approved the manuscript.

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Data-sharing statement

Data can be shared upon reasonable request in an anonymized form.

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