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Research article

No impact of steatotic liver disease on clinical outcomes in patients with essential thrombocythemia and polycythemia vera: A pilot study

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ABSTRACT

The presence of steatotic liver disease (SLD) is associated with an increased cardiovascular risk in the general population. Chronic myeloproliferative neoplasms (MPNs), essential thrombocythemia (ET) and polycythemia vera (PV), are characterized by clonal myeloproliferation, chronic inflammatory state, and increased cardiovascular morbidity and mortality. The aim of this single-center study was to analyze clinical associations and the potential prognostic impact of SLD in ET and PV patients. We retrospectively included 108 patients (64 ET and 44 PV); median age was 70.5 years (range 21–92), 68 (63 %) were females, and the median follow-up time was 69 months. Baseline SLD presence was defined ultrasonographically and was detected in 25 (23.1 %) patients. There were no associations of SLD with any of the clinical and laboratory patient characterictics. Also, baseline ultrasonographic presence of SLD did not have an impact on future thrombotic, bleeding and disease transformation risk, nor patient survival. None of the patients experienced signs of liver failure during the follow-up. In conclusion, the presence of SLD in ET and PV patients does not seem to have major clinical implications. Therefore, patients may be advised about the generally harmless nature of SLD when occurring in the MPN context.

1. Introduction

Steatotic liver disease (SLD) may be considered as a hepatic manifestation of metabolic syndrome, as it is associated with arterial hypertension, hyperlipidemia, and diabetes mellitus. It affects ~25 % of adults and promotes cardiovascular disease [1] and the development of different cancers [2]. SLD is an umbrella term which covers several entities: metabolic dysfunction associated liver

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disease (MASLD), MASLD with an increased alcohol uptake, alcohol associated liver disease, specific SLD (i.e, Wilson disease, inborn errors of metabolism, viral hepatitis) and cryptogenic SLD [3]. The golden diagnostic standard for SLD is liver biopsy; however, it is not mandatory for all patients with suspected disease, as it is costly, invasive, and not without risk. Therefore, liver biopsy is usually recommended to assess the risk of fibrosis and disease progression and to rule out concomitant liver disorders [4,5]. For this reason, clinicans often rely on liver ultrasound to detect SLD, especially in the absence of other suspected liver disorders, as its sensitivity and specificity is quite high (>80 %) [5].

Essential thrombocythemia (ET) and polycythemia vera (PV) are chronic myeloproliferative neoplasms (MPNs) characterized by acquired mutations in the Janus Kinase 2 (JAK2) or calreticulin (CALR) genes which cause clonal myeloproliferation, chronic inflammatory state, and an increased risk of thrombosis and bleeding [6–9]. Additionally, MPNs have an intrinsic tendency to transform to secondary myelofibrosis (SMF) and acute myeloid leukemia (AML) [10]; these events significantly affect patients' survival but the risk of thrombosis and bleeding still dominates the clinical course in MPNs [11,12].

As MPNs are characterized by a chronic inflammatory state triggering cardiovascular complications and promoting cancer development and progression [13] this pilot study aimed to investigate clinical associations and the potential prognostic impact of SLD in ET and PV.

2. Patients and methods

This was a single-center study conducted at General Hospital Sibenik, Croatia, in the period from 2000 to 2022. ET and PV patients whose disease diagnosis was reassessed according to 2016 World Health Organization criteria [14] and who had available ultrasonographic data regarding SLD at the time of MPN diagnosis were retrospectively included. None of the patients included had a history of excess alcohol intake, viral or autoimmune hepatitis, hereditary and inborn metabolic liver diseases. Also, none of the patients included underwent liver biopsy; nevertheless, this study primarily focused on the clinical relevance of ultrasonographic SLD presence in MPNs.

The presence of SLD was defined by licensed radiologists and was recorded as such in the medical documentation. Abdominal ultrasound was performed in all patients after overnight fasting, in supine position or in the left decubital position. In grey scale, fatty SLD looks brighter than the renal cortex. With the increased accumulation of liver fat, ultrasound waves become more attenuated, which results in decreased visualization of the deeper parts of the liver (diaphragm and hepatic veins). Therefore, diagnosis of SLD was based on the increased echogenicity of the liver parenchyma in comparison to the right renal cortex [4,5].

Clinical and laboratory data was also collected through medical chart review and was recorded at the time of disease diagnosis. Specific cardiovascular comorbidities of interest were arterial hypertension, diabetes mellitus, hyperlipidemia and smoking („active/

Table 1
Patient characteristics stratified according to presence of steatotic liver disease (SLD). The chi-squared, the Mann-Whitney U and the one-way analysis of variance (ANOVA) tests were used.

Variable	Overall (n = 108)	SLD (n = 25, 23.1 %)	No SLD (n = 83, 76.9 %)	p value
Sex, female	68 (63 %)	12 (48 %)	56 (67.5 %)	0.078
Age, years (median, range)	70.5 (21–92)	71 (46–87)	70 (21–92)	0.656
ET	64 (59.3 %)	15 (60 %)	49 (59 %)	0.931
PV	44 (40.7 %)	10 (40 %)	34 (41 %)	
JAK2-V617F	75 (69.4 %)	16 (64 %)	59 (71.1 %)	0.793
Calreticulin	26 (24.1 %)	17 (28 %)	19 (22.9 %)	
Negative	7 (6.5 %)	2 (8 %)	5 (6 %)	
Prior thrombosis	25 (23.1 %)	7 (28 %)	18 (21.7 %)	0.513
Palpable splenomegaly	30 (27.8 %)	5 (20 %)	25 (30.1 %)	0.324
Constitutional symptoms	31 (28.7 %)	6 (19.4 %)	19 (24.7 %)	0.550
Arterial hypertension	75 (69.4 %)	19 (76 %)	56 (67.5 %)	0.419
Hyperlipidemia	41 (38 %)	9 (36 %)	32 (38.6 %)	0.818
Diabetes mellitus	15 (13.9 %)	5 (20 %)	10 (12 %)	0.315
Smoking	7 (6.5 %)	1 (7.2 %)	6 (4 %)	0.567
Hydroxyurea	91 (84.3 %)	19 (76 %)	72 (86.7&)	0.197
Aspirin	66 (61 %)	17 (68 %)	49 (59 %)	0.422
Total leukocytes, $x10^9$/L (median, range)	9 (4.4–36.4)	9.4 (6.3–20.7)	8.8 (4.4–36.4)	0.590
Erythrocytes, $x10^{12}$/L (median, range)	5.06 (±1.2)	5.21 (±1.18)	5.01 (±1.21)	0.459
Hematocrit, % (median, range)	46.6 (27.8–90)	46.6 (31.7–53.3)	46.6 (27.8–90)	0.580
Hemoglobin, g/L (median, range)	143.7 (±25)	141.6 (±21.4)	144.3 (±26.7)	0.645
Platelets, $x10^9$/L (median, range)	551 (40–3211)	516 (186–1804)	558 (40–3211)	0.306
Serum aspartate aminotransferase, IU/L (median, range)	22 (13–52)	22 (13–52)	22.5 (14–36)	0.482
Serum alanine aminotransferase, IU/L (median, range)	24 (9–76)	19 (8–69)	24 (9–76)	0.039
Serum gamma-glutamyl aminotransferase, IU/L (median, range)	22 (6–181)	22 (6–181)	24 (10–162)	0.252
Serum alkaline phosphatase, IU/L (median, range)	73.5 (40–164)	72 (40–153)	79 (45–164)	0.792
Serum total cholesterol, mmol/L (median, range)	4.3 (1–9.6)	4.3 (1–9.6)	4.5 (1.9–6.9)	0.279
Serum low-density lipoprotein, mmol/L (median, range)	2.4 (0.65–4.93)	2.37 (0.65–4.77)	2.5 (1.6–4.93)	0.199
Serum high-density lipoprotein, mmol/L (median, range)	1.2 (0.19–2.3)	1.19 (0.19–2)	1.38 (0.8–2.3)	0.133
Serum triglycerides, mmol/L (median, range)	1.4 (0.3–3.7)	1.2 (0.4–2.6)	1.3 (0.6–3.7)	0.249

SLD = steatotic liver disease, ET = essential thrombocythemia, PV = polycythemia vera.

prior vs. „never"). Constitutional symptoms were defined as the presence of fatigue, night sweats, fevers, or weight loss (>10 % of body weight in the preceding 6 months).

Statistics were performed with licensed MedCalc Software® (Ostend, Belgium, version 22.016). Shapiro-Wilk's test was used to check for data distribution. Categorical variables were compared using the chi-squared test, whereas continuous variables were compared with the Mann-Whitney U or one-way analysis of variance (ANOVA) tests, as appropriate. Survival analyses were perfomed with the Kaplan-Meier method and the log-rank test. Time to thrombosis (composite arterial/venous thrombotic event), time to bleeding, time to disease transformation (SMF, AML, or myelodysplastic syndrome-MDS) and overall survival were measured from the time of diagnosis until the date of an event of interest. Arterial thrombotic events considered were acute myocardial infarction, transitory ischemic attack, ischemic stroke or acute peripheral arterial occlusion; venous thrombotic events of interest were pulmonary embolism and/or deep vein thrombosis. Statistically significant p values were set at <0.050 for all presented analyses.

3. Results

A total of 115 ET and PV patients were diagnosed at our institution during the aforementioned period (2000–2022); 108 MPN (64 ET, 44 PV) had available ultrasound assessments and were thus included in this analysis. The median age was 70.5 years (range 21–92), 68 (63 %) were females, and SLD was detected in 25 (23.1 %) patients. Patient's characteristics stratified according to SLD presence are presented in Table 1. As shown, aside from the lower serum alanine aminotransferase levels in patients with SLD (median 19 vs 24 IU/L, p = 0.039), there were no statistically significant associations of SLD with any of the clinical and laboratory variables in ET and PV (p > 0.050 for all analyses). Interestingly, none of the cardiovascular risk factors were associated with SLD presence, neither individually nor stratified as the presence of any cardiovascular risk factor (p > 0.050 for all analyses).

The median follow-up was 69 months (range 1–307); 26 (24,1 %) thrombotic events (arterial, n = 16, venous, n = 10), 15 (13.9 %) bleedings (gastrointestinal, n = 6, nosebleeds, n = 5, hemoptoa, n = 2, prolonged bleeding after tonsillectomy, n = 1, prolonged bleeding after tooth extraction, n = 1), 9 (8.3 %) disease transformations (SMF, n = 7, AML, n = 1, MDS, n = 1), and 40 (37 %) deaths (cardiovascular causes, n = 8, infection, n = 5, secondary solid cancers, n = 3, disease transformation, n = 3, dementia, n = 2, chronic obstructive pulmonary disease, n = 2, haemorrhagic shock secondary to gastrointestinal bleeding, n = 1, unknown, n = 16) occurred during this time. As depicted in Fig. 1, the presence of SLD did not have an impact on thrombosis (Fig. 1a), bleeding (Fig. 1b), disease transformation (Fig. 1c), nor survival (Fig. 1d). Also, SLD did not affect these clinical outcomes when ET and PV were analyzed separately (p > 0.050 for all analyses). None of the patients included in the study developed clinical and/or laboratory signs of liver failure (coagulopathy, hypoalbuminemia, oesophageal varices, ascites, encephalopathy) during the follow-up.

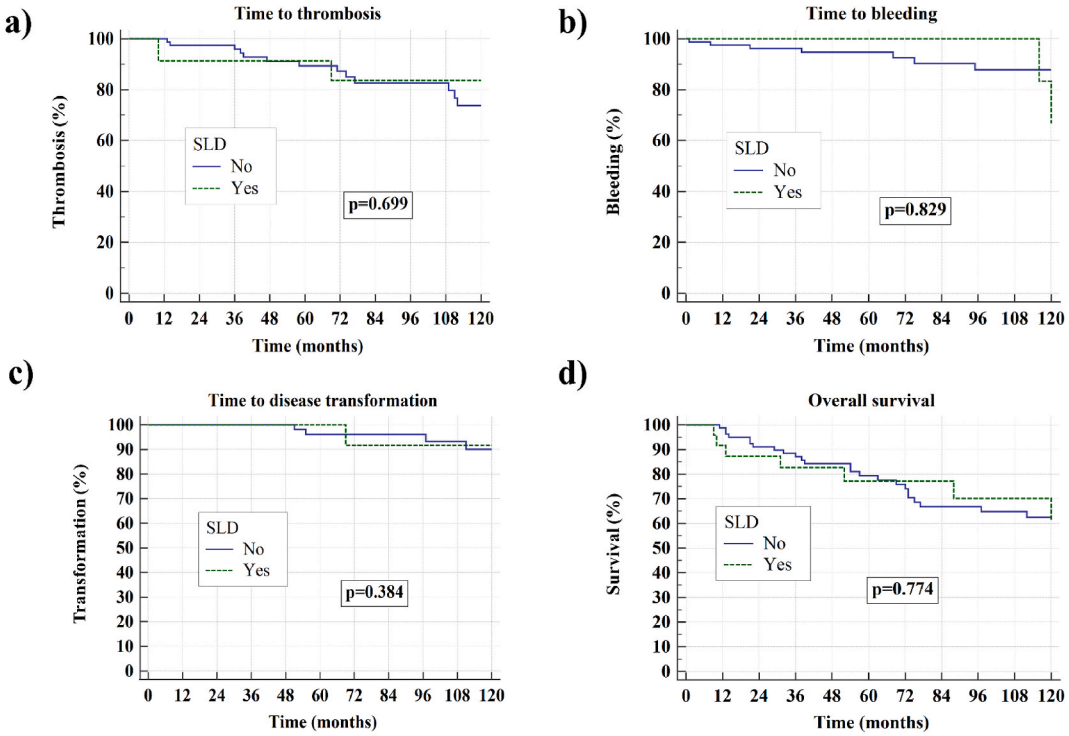

Fig. 1. Time to thrombosis (a), time to bleeding (b), time to disease transformation (c) and overall survival (d) in patients with essential thrombocythemia and polycythemia vera stratified according to presence of steatotic liver disease (SLD). The Kaplan-Meier method and the log-rank test were used.

4. Discussion

Similarly to ET and PV patients who are burdened with various debilitating disease-related symptoms [15], patients with SLD in the general population also show higher levels of anxiety, depression, and worry [16,17]. As SLD has been associated with an increased cardiovasular risk as well as with the development of different cancers in the general population [1,2] uncertainties regarding the clinical relevance of SLD in MPN patients often come up in the physician's office. For this reason we found it relevant and timely to assess the prognostic impact of SLD in MPNs. Unfortunately, due to the retrospective design of our study we were not able to ultrasonographically assess all ET and PV patients for baseline SLD presence. On the other hand, later assessments for SLD and their classification as such would also unevitably lead to the risk of immortalization during survival analyses. For this reason, we intentionally focused on SLD presence at the time of MPN diagnosis. Our observations suggest that the frequency of baseline ultrasonographic SLD presence in ET and PV patients may be quite similar to that of the adult general population which is ~25 [1]. More importantly, the presence of SLD did not seem to affect important MPN-related outcomes. Additionally, none of the MPN patients experienced signs of liver failure during the study follow-up. Accordingly, ET and PV patients may be counseled about the general harmless nature of SLD when occurring in the MPN context. Interestingly, none of the MPN-related clinical and laboratory ariables were associated with SLD presence, nor was the presence of generic cardiovascular risk factors or blood lipids. Again, due to the retrospective design and the missing data we could not additionally analyze clinical associations of SLD with body weight, body height and body mass index. We would also like to point out that different cardiovascular risk factors in MPN patients (i.e, arterial hypertension, hyperlipidemia, diabetes mellitus, hyperuricemia etc.) may have their own specificities and that their treatment strategies may potentially differ from that in the general population [7,18]. Moreover, MPN patients are usually closely followed by hematologists in routine clinical practice with the stringent control of cardiovascular risk factors, frequent use of antiplatelets/anticoagulants and different cytoreductive medications; these treatments could have potentially modified the effect of SLD on clinical variables and outcomes in the MPN context. Indeed, there are similar signals suggesting a potentially protective effect of cytoreduction in non-MPN patients suffering from acute thrombotic events [19–23] but further studies on this topic are warranted. Nevertheless, lifestyle modifications, such as weight loss, healthy diet, and regular physical activity should be recommended to all MPN patients with SLD. Additionally, stringent control of generic cardiovascular risk factors should be strongly encouraged [4,7].

Limitations of the presented study are its retrospective single-center design, small number of patients included, low number of events of interest, and the lack of baseline and longitudinal ultrasonographic SLD grading assessments during disease follow-up to assess whether different degrees of SLD and the evolution of SLD may potentially have an impact on clinical outcomes in this patient population. Therefore, further studies on larger number of MPN patients are needed to confirm our findings and to focus on these remaining issues.

Ethics

The study was performed in accordance with Helsinki Declaration and was approved by the Ethics Committee of General Hospital of Sibenik-Knin County, Croatia (reference number 01–3618/1-20, date February 26, 2020). Due to retrospective study design, informed consent was waived by the Ethics Committee.

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Data availability statement

The data generated in this study are available on reasonable request to the corresponding author.

CRediT authorship contribution statement

Ivan Krečak: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Josipa Antonija Bačić:** Writing – review & editing, Investigation. **Nevena Šimunić:** Writing – review & editing, Writing – original draft, Investigation. **Vesna Bušac:** Writing – review & editing, Investigation. **Ljerka Pivac:** Writing – review & editing, Investigation. **Eva Čubrić:** Writing – review & editing, Investigation. **Marko Skelin:** Writing – review & editing, Writing – original draft, Conceptualization. **Marko Lucijanić:** Writing – review & editing, Writing – original draft, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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