„CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
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MEDICINE

Novel approaches to BCR::ABL1-negative myeloproliferative neoplasms: the assessment of oxidative stress and quality of life

PhD THESIS SUMMARY

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Introduction

Myeloproliferative neoplasms (MPNs) are clonal disorders of the hematopoietic stem cells characterized by a hyperproduction of myeloid cells irrespective of the concentrations of hematopoietic growth factors. MPNs can be classified based on the presence or absence of molecular biomarkers into *BCR::ABL1*-positive MPNs (a category that includes only one entity, i.e., chronic myeloid leukemia) and *BCR::ABL1*-negative MPNs. *BCR::ABL1*-negative MPNs comprise classical MPNs, non-classical MPNs (chronic neutrophilic leukemia, chronic eosinophilic leukemia, juvenile myelomonocytic leukemia), and an unclassifiable MPN. The current PhD thesis is solely focused on classical *BCR::ABL1*-negative MPNs (termed MPNs from now on): polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)(Khoury, 2022; Arber, 2022).

MPNs are characterized by somatic driver mutations in genes involved in the JAK-STAT signaling pathway which influences hematopoiesis, namely the *JAK2*, *CALR*, and *MPL* genes. Genetic abnormalities occurring in these genes can reproduce the MPN phenotype from humans to *in vivo* models. Apart from these genetic lesions, additional mutations may develop in MPNs, e.g., in genes involved in epigenetic regulation (*DNMT3A*, *TET2*, *ASXL1*, *IDH1*, *IDH2*, *EZH2*) or genes coding for transcription factors (*RUNX1*, *TP53*, *NFE2*), genetic abnormalities which are not able to reproduce the MPN phenotype *in vivo*, however, they can alter the phenotype caused by driver mutations. MPNs are associated with an elevated rate of thrombotic and sometimes hemorrhagic events, as well as a predisposition of PV and ET to transform into secondary myelofibrosis (SMF), as well as of all MPNs to progress to secondary acute myeloid leukemia (sAML). The pathogenesis of MPNs is complex and revolves not only around genetic factors but also around the contribution of other molecular mechanisms, such as oxidative stress (OS), chronic inflammation, alterations of the gut microbiota, and others. The clinical presentation of MPN patients is dominated by the presence of constitutional, vascular and organ-related symptoms which negatively impact the quality of life (QoL) of the subjects living with these conditions. Moreover, cardiovascular risk factors (CVRF), such as primary arterial hypertension (HTN), type 2 diabetes mellitus (T2DM), dyslipidemia and metabolic syndrome increase the risk of thrombosis and contribute to the burden of disease in MPNs, reducing the patients' QoL even further (Liongue, 2024; Tashkandi, 2024; Tefferi, 2023; Kelliher, 2021;

Găman, 2021; Wille, 2023; Găman, 2023a; Găman, 2023b; Găman, 2024a; Găman, 2024b; Găman, 2024c; Manan, 2023; Pîrciulescu, 2022; Barbui, 2023; Loscocco, 2024; Morales, 2023).

The goal of the current PhD thesis was to put forth novel approaches to MPNs, and its **main objectives** consisted of the assessment of OS and QoL in these hematological malignancies. Its **secondary objective** was to investigate the impact of CVRF on the rate of thrombotic events and MPN evolution. The PhD thesis is structured into two parts, the background which reports on the current state of knowledge, and the personal contributions part which consists of the results of three distinct studies that have explored the aforementioned research pathways. The PhD thesis consists of **10 chapters**, as well as a list of references with over 550 titles.

Background – Current state of knowledge

The current state of knowledge comprises three chapters that are focused on an overview of MPNs, the molecular mechanisms involved in MPN pathogenesis, and data related to the QoL of MPN patients.

Chapter 1 begins with the most recent classification of myeloid neoplasms and MPNs, and sheds light on the epidemiology, pathogenesis, clinical presentation, laboratory work-up, treatment strategies, as well as the evolution, complications, and prognosis of MPNs, in agreement with international guidelines and the most recent classifications of the World Health Organization and International Consensus Classification (Khoury, 2022; Arber, 2022; Gerds, 2022; Tefferi, 2024; Tefferi, 2023a; Tefferi, 2023b; Gianelli, 2023; Găman, 2024d).

Chapter 2 revolves around the molecular mechanisms involved in MPN pathogenesis, highlighting the role of genetic factors (driver mutations in the *JAK2*, *CALR*, and *MPL* genes, as well as additional non-driver mutations), OS, chronic inflammation, alteration of the gut microbiome, as well as other phenomena that influence the development and evolution of these malignancies (Luque Paz, 2023; Constantinescu, 2021; Easwar, 2021; Adesola, 2023; Adesola 2024).

Chapter 3 is focused on the methods employed to assess QoL and symptom burden in MPNs, detailing the main psychometric instruments developed to assess QoL in these disorders, as well as on the presentation of the MPN-10 questionnaire (Emanuel, 2012; Tremblay, 2022; Mesa, 2021; Mesa, 2023).

Personal contributions

The personal contributions section is structured into five chapters which follow three research pathways: the involvement of OS and the genetic landscape, as well as their interplay, in MPNs, the assessment of QoL and symptom burden in MPNs, and the translation, cultural adaptation and validation to Romanian of the MPN-10, as well as the contribution of CVRF to the occurrence of thrombotic events in these hematological malignancies.

Chapter 4 shares the hypothesis and main objections of the PhD thesis, whereas **Chapter 5** introduces the methodology of the current research (the approach to the research questions and to ethics).

The main objectives of the doctoral research were:

1. To assess OS in MPNs in their chronic phase and blast phase (sAML) in order to establish potential correlations with the genetic landscape of MPN patients, as well as to evaluate the contribution of OS to MPN progression towards SMF and sAML.
2. To translate, culturally adapt, and validate the MPN-10 to Romanian to provide hematologists with a useful and accurate instrument to assess QoL and symptom burden in MPNs to establish timely therapeutic interventions and improve QoL among MPN patients
3. To identify additional CVRF that can elevate the risk of thrombosis in MPNs to accurately manage comorbidities in MPNs, reduce cardiovascular risk as well as the rates of death due to thrombosis in these patients

Chapter 6, entitled „***Study no. 1: Assessment of total antioxidant capacity, 8-hydroxy-2'-deoxy-guanosine, the genetic landscape and their associations in chronic and blast phase classical BCR::ABL1-negative MPNs"***, overviews the results of an observational study which also included an experimental part and that was conducted between March 2023 and March 2024. The study included 117 subjects with MPNs (PV, ET, PMF), 21 with sAML (blast phase MPNs) and a control group of 14 healthy volunteers (Găman, 2024a). To establish the genetic landscape of MPN patients, peripheral blood samples were collected from which granulocyte DNA was isolated. All individuals were screened for the presence of driver mutations in the *JAK2*, *CALR*, and *MPL* genes, whereas extensive genetic testing (NGS, WES, SNP array) was conducted in selected cases (mainly sAML). OS was assessed *via* ELISA by quantification of 8-hydroxy-2'-deoxy-guanosine (8-OHdG) as a biomarker of oxidative injury to the DNA and

of the total antioxidant capacity (TAC). Statistical analysis was carried out using the JASP software version 0.18.3.0.

The study was conducted in agreement with the Declaration of Helsinki in the Department of Cellular and Molecular Pathology, "Ştefan S. Nicolau" Institute of Virology, Romanian Academy, Bucharest, and was approved by the local Ethics Committee (approval no. 192/06.02.2023). All enrolled subjects were notified about the investigation, agreed to partake, and signed the written informed consent form. Biological samples were anonymized and stored in the biobank of the Institute of Virology where the "Molecular Profiling of Myeloproliferative Neoplasms and Acute Myeloid Leukemia for Designing Early Diagnostic, Prognostic and Treatment Strategies (MYELOAL – EDIAPROT)" grant (Competitiveness Operational Programme 2014-2020 A1.1.4. ID: P_37_798 MyeloAL-EDiaProT, contract 149/26.10.2016, MySMIS2014+: 106774, MyeloALProject) was implemented.

Regarding the **results of study no. 1**, we enrolled 117 cases of MPNs, 21 cases of sAML and 14 healthy volunteers. Patients with MPNs were diagnosed with PV (n = 29; 25.00%), ET (n = 40; 34.00%) or PMF (n = 48; 41.00%). PMF subjects suffered either from prefibrotic PMF (prePMF)(n = 12; 10.25%) or overt fibrotic PMF (n = 36; 30.75%). The demographical, clinical, and laboratory parameters of the study group are listed in **Table 1**.

Table 1. MPNs and sAML patients' demographics and clinical/laboratory data

Characteristics	**Controls**	**MPNs**	**PV**	**ET**	**PMF**	**sAML**
Number of patients	14	117	29	40	48	21
Age (years)	55.00±10.00	57.92±15.31	55.10±16.37	55.23±16.68	61.85±12.70	61.76±8.77
Sex (female), %	58%	58.12%	51.72%	75%	47.92%	47.62%
Leukocytes x 10^9/L	4.5-9	14.23±9.82	16.96±16.21	14.70±8.41	10.08±5.96	48.88±95.46
Hemoglobin g/dL	12-13	12.09±3.51	14.83±2.02	12.72±3.57	11.65±3.58	14.83±2.02
Platelets x 10^9/L	150-400	634.9±567.0	659.3±471.2	735.6±725.8	545.5±465.3	761.2±377.7
JAK2V617F (%)	0.00%	71.80%	100.00%	65%	60.42%	52.38%
CALR type 1/2 (%)	0.00%	17.95%	0.00%	22.50%	25%	19.05%
MPLW515L (%)	0.00%	6.84%	0.00%	7.50%	2.08%	0.00%
Triple-negative (%)	0.00%	3.41%	0.00%	5.00%	12.50%	28.57%
Treatment-naïve MPNs	0.00%	88.03%	96.55%	90.00%	81.25%	61.90%
History of thrombosis	0.00%	4.27%	5.00%	0.00%	4.17%	9.52%
CVRF	0.00%	8.55%	10.34%	5.00%	8.33%	23.81%

Legend: MPNs, classical *BCR::ABL1*-negative myeloproliferative neoplasms. PV, polycythemia vera. ET, essential thrombocythemia. PMF, primary myelofibrosis. sAML, secondary acute myeloid leukemia. CVRF, cardiovascular risk factors.

Extensive genetic testing using NGS, WES and/or SNP array was carried out in selected cases, in particular in patients with sAML. The main results of these assessments, in correlation with TAC and 8-OHdG levels, are reported in **Table 2**.

Table 2. Interplay between MPNs/sAML, OS, and the genetic landscape

Diagnosis	Age (years), sex	Previous treatment	CAT	8-OHdG	M-ain results of the genetic testing
PV	33, M	No	6.14	0.57	Driver mutation: JAK2 V617F 88% TP53 c.388C>T, p.(L130F), 35%, loss of function, COSM11449 BCOR c.4938_4939delCT, p.(L1647fs*4), 42%, loss of function, likely pathogenic, (unreported)
PV	65, F	No	5.15	0.51	Driver mutation: JAK2 V617F Targeted NGS: negative for other mutations
prePMF	26, F	No	4.87	0.58	Driver mutation: triple-negative NF1 c.1792A>C (K598Q), 30%, missense, probably damaging
PMF	48, F	RUX	5.29	0.58	Driver mutation: JAK2 V617F 92.8%; TET2 c.593dupT, 33.5%, rs748109142, unknown significance; ASXL1 c.1934dupG (p.G646Wfs*12), 32.1%,COSM1411076
PMF	51, F	ANA	4.99	0.50	Driver mutation: CALR type 2 CALR c.1154_1155ins TTGTC 45.2% TET2 c.4354C>T p.R1452* (nonsense) 21% COSM41706
PMF	68, F	No	7.00	16.35	Driver mutation: CALR type 1 NRAS c.190T>G (p.Y64D) 44.8%, COSM1666991 PTNP11 c.1516T>A (p.S502T) 21.4%, COSM14258
post-PMF sAML	72, F	HU	6.65	0.94	Driver mutation: JAK2 V617F (DNA from CD34+ cells: 6%, DNA from CD3+ cells: 2.5%) TET2 c.1648C>T p.R550*, COSM41644 (DNA from CD34+ cells: 48.6%, DNA from CD3+ cells: 37.8%) ASXL1 c.2066C>G, p.S689*, COSM133037 (DNA from CD34+ cells: 43%, DNA from CD3+ cells: 35.4%) STAG2 c.1840C>T, p.R614*, COSM166815 (DNA from CD34+ cells: 40.9%, DNA from CD3+ cells: 33.9%) TET2 c.5611_5618delATTCTCAT, p.I1871Ter, unreported; (DNA from CD34+ cells: 36.8%, DNA from CD3+ cells: 36.5%) IDH2, c.419G>A, p.R140Q, COSM41590 (DNA from CD34+ cells: 27.2%, DNA from CD3+ cells: 19.70%)
post-ET sAML	76, F	HU	5.44	0.52	Driver mutation: JAK2 V617F 78.9% DNMT3A c.2322+1G>A, p.? splice-site mutation pathogenic 43%
post-PMF sAML	51, F	AZA	6.47	0.52	Driver mutation: JAK2 V617F (DNA from CD34+ cells: 72%; DNA from CD3+ cells: 10%) TP53 c.537T>A, p.179Q, missense, COSV52669519 (DNA from CD34+ cells: 100%; DNA from CD3+ cells: 35%) SRSF2 c.284C>T, p.P95L, missense, COSV57969830 (DNA from CD34+ cells: 49%; DNA from CD3+ cells: 12%)
post-PMF sAML	54, F	ANA	6.82	0.52	Driver mutations: CALR type 1 FLT3 57.2% (unknown clinical significance, extremely rare in general population) ASXL1 c.2476_2485 dupGGAACTGGCC 28.2% unreported
post-PMF sAML	56, M	HU	5.75	0.49	Driver mutation: triple-negative ASXL1 c.1888_1910del23 (p.E635fs*15) 73.7% COSM36165 TP53 c.395A>G (p.K132R) 66.3% COSM308311 EZH2 c.1979G>A (p.G660E) 39.5% (unreported in COSMIC, deleterious/probably damaging)
post-PMF sAML	50, F	RUX	5.53	0.51	Driver mutation: JAK2 V617F TET2 c.1088C>T (p.P363L) 48.4%, COSM5020142 (germline, clinical significance not provided KIT c.1621A>C (p.M541L), 52.1%, COSM28026

post-PMF sAML	69, F	No	4.90	0.51	Driver mutation: CALR type 1 51% NRAS c.190T>G, p.Y64D, (DNA from CD34+ cells: 90.9%; DNA from CD3+ cells: 49% - germline) NRAS c.35G>A, p.G12D, 43%, COSM564 SNP array: del7q22.1, del8q11.1-q11.21, del10p12.1-p11.22, del11p14.1-p11.2, delXp11.4 UPD1p
post-PMF sAML	63, M	AZA	6.45	0.51	Driver mutation: JAK2 V617F (DNA from CD34+ cells: 95.1%; DNA from CD3+ cells: 17.8%) RUNX1 c.364_365insAA, frameshift, p.Gly122fsTer12 (DNA from CD34+ cells: 60.9%; DNA from CD3+ cells: 14.8%) CSF3R c.2492C>T, p.A831V (unreported) (DNA from CD34+ cells: 47.4%) IDH1 c.395G>A, p.R132H, COSM28746 (DNA from CD34+ cells: 34.4%; DNA from CD3+ cells: 5.00%) PHF6 c.385C>T. p.R129*, COSM4606367 (DNA from CD34+ cells: 6.00%)
post-PMF sAML	57, F	No TAC	6.37	0.51	Driver mutation: triple-negative sAML: FLT3-ITD
post-PMF sAML	57, M	No	5.27	0.52	Driver mutation: CALR type 1 58.1% SNP array: UPD11q Targeted NGS: DNA from PBMC ASXL1 c.1773C>A, p.Y591*, 49.3%, COSM1681609 CBL c.1111T>A, p.Y371N, 93.1%, COSM5031014 DNA from granulocytes ASXL1 c.1773C>A, p.Y591*, 43.9%, COSM1681609 CBL c.1111T>A, p.Y371N, 98%, COSM5031014 WES: DNA from PBMC CALR del52 39% ASXL1 c.1773C>A, p.Y591*, 49%, COSM1681609 CBL c.1111T>A (p.Y371N), 96%, COSM5031014 NBN c.511A>G, p.I171V, missense unknown significance, 55% STAT5A c.2118dupT, p.V707fs, 56%

Legend: TAC—total antioxidant capacity, 8-OHdG—8-hydroxy-2′-deoxy-guanosine, MPNs—myeloproliferative neoplasms, sAML—secondary acute myeloid leukemia, PV—polycythemia vera, ET—essential thrombocythemia, MF—myelofibrosis, prePMF—prefibrotic primary myelofibrosis, PMF—primary myelofibrosis, Obs.—Observation(s), OS—oxidative stress, HU—hydroxyurea, AZA—azacytidine, RUX—ruxolitinib, ANA—anagrelide, NGS—next-generation sequencing, WES—whole-exome sequencing, PBMC—peripheral blood mononuclear cells, DNA—deoxyribonucleic acid, and SNP—single nucleotide polymorphism.

TAC was higher in MPNs versus controls (6.05 ± 1.11 vs. 5.46 ± 0.65, P=0.03); however, TAC was similar between controls and sAML (5.46 ± 0.65 vs. 5.99 ± 1.05, P=0.10) or sAML and MPNs (6.05 ± 1.11 vs. 5.99 ± 1.05, P=0.83) (**Figure 1**).

TAC was elevated in ET (6.12 ± 1.11 vs. 5.46 ± 0.65, P=0.04) and PMF (6.11 ± 1.23 vs. 5.46 ± 0.65, P=0.02) (**Figure 2**), particularly in fibrotic PMF (6.25 ± 1.30 vs. 5.46 ± 0.65, P=0.01; **Figure 3**). CAT was similar between controls and PV (P=0.21) and prePMF (P=0.52).

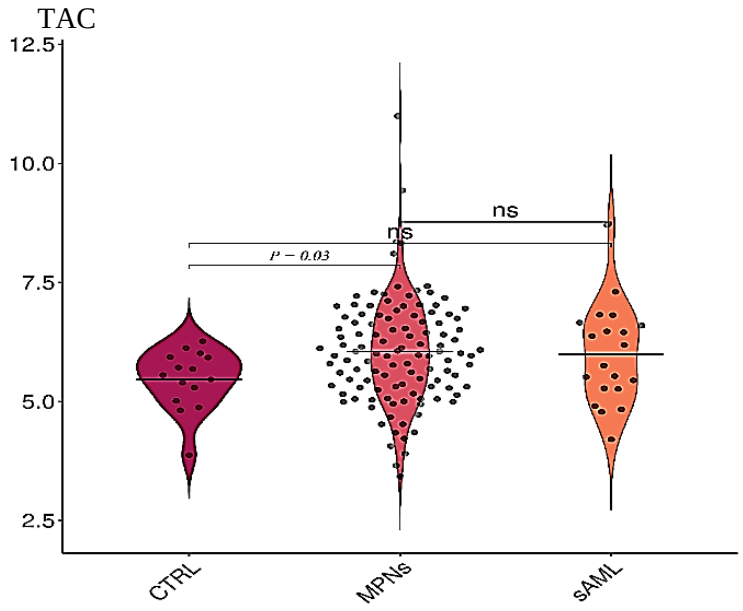


Figure 1. TAC evaluation in MPNs and sAML versus controls.

(source: original figure – see Găman, 2024a)

Legend: CTRL, controls, MPNs, myeloproliferative neoplasms, sAML, secondary acute myeloid leukemia, ns, not significant.

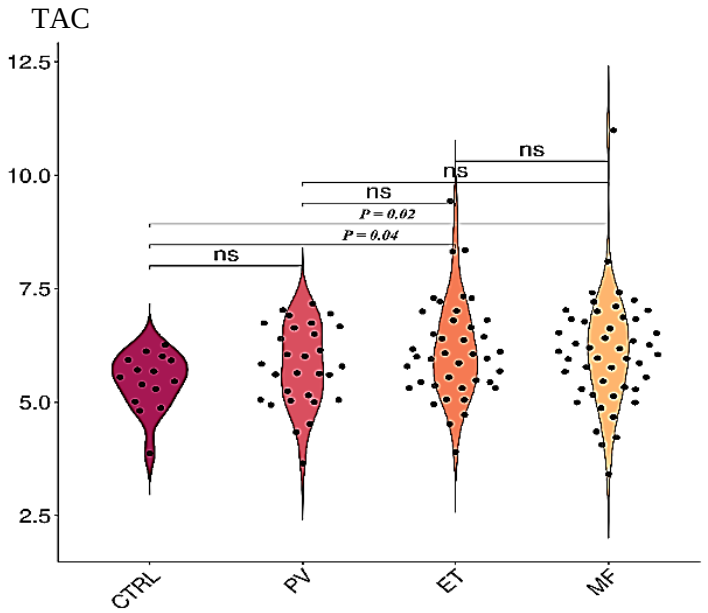


Figure 2. TAC evaluation in MPNs versus controls.

(source: original figure – see Găman, 2024a).

Legend: CTRL, controls, PV, polycythemia vera. ET, essential thrombocythemia. MF, primary myelofibrosis

MPLW515L-positive MPNs had higher TAC versus controls (6.74 ± 0.49 vs. 5.46 ± 0.65, P=0.002) and triple-negative MPNs (6.74 ± 0.49 vs. 5.43 ± 0.82, P=0.01). In particular, TAC

was elevated in *MPLW515L*-positive ET versus controls (6.90 ± 0.45 vs. 5.46 ± 0.65, P=0.002) and triple-negative ET (6.90 ± 0.45 vs. 5.58 ± 0.39, P=0.04). Moreover, fibrotic PMF cases who had received MPN treatment had lower TAC versus treatment-naïve patients (5.43 ± 0.99 vs. 6.50 ± 1.24, P=0.03). Despite our suppositions, age, sex, specific therapies or CVRF did not influence TAC in MPNs or sAML. We did not detect any association between TAC and 8-OHdG, age, driver mutations' allele burden, bone marrow fibrosis grade, leukocyte/platelet counts or hemoglobin levels in MPNs or sAML.

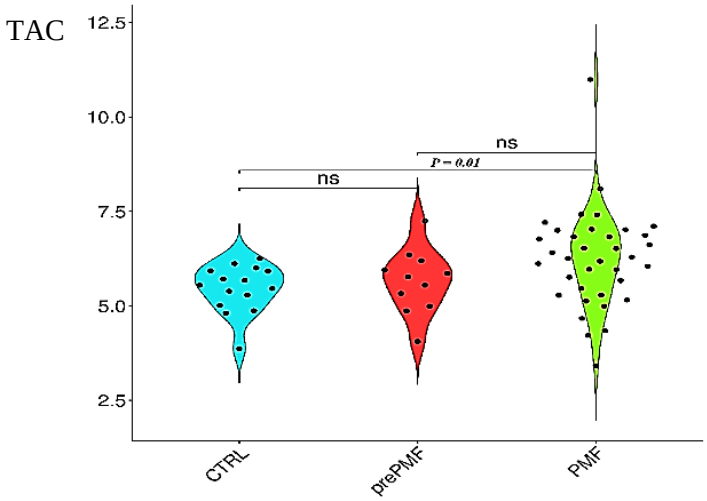


Figure 3. TAC evaluation in prePMF and PMF versus controls (source: original figure – see Găman, 2024a).

Legend: CTRL, controls. prePMF, prefibrotic PMF, PMF, fibrotic PMF.

8-OHdG was similar between controls and MPNs (0.62 ± 0.12 vs. 0.97± 1.91, P=0.59), irrespective of subtype, and sAML (0.62 ± 0.12 vs. 0.92 ± 1.11, P=0.67), as well as between MPNs and sAML (0.97 ± 1.91 vs. 0.92 ± 1.11, P=0.91). No correlations between 8-OHdG and age, sex, bone marrow fibrosis grade or other parameters were noted in MPNs or sAML.

Univariate regression revealed an association between TAC and MPNs (OR = 1.82; P=0.05), and in particular ET (OR = 2.36; P=0.03) and fibrotic PMF (OR = 2.11; P=0.03), but not between sAML and TAC. 8-OHdG was associated with neither diagnosis: MPNs (OR =1.73; P=0.62) or sAML (OR = 1.89; P=0.49).

Data regarding OS assessment in MPNs, sAML and controls based on the genetic landscape is listed in **Table 3**.

Table 3. OS evaluation in MPNs and sAML based on the presence of driver mutations

Subgrupuri	TAC (Trolox equivalent)	8-OHdG (ng/mL)
Controls	5.46 ±0.65	0.62 ± 0.12
MPNs (entire cohort)	6.05 ± 1.11	0.97 ± 1.91
sAML	5.99 ± 1.05	0.92 ± 1.11
PV	5.79 ± 0.89	0.81 ± 0.62
JAK2V617F (+)	5.79 ± 0.89	0.81 ± 0.62
EE	6.12 ± 1.11	0.56 ± 0.09
JAK2V617F (+)	6.15 ± 1.25	0.54 ± 0.10
CALR (+)	6.04 ± 0.77	0.58 ± 0.10
MPLW515L (+)	6.90 ± 0.45	0.58 ± 0.09
Triple-negative	5.58 ± 0.38	0.57 ± 0.08
PMF	6.11 ± 1,23	1.27 ± 2.94
JAK2V617F (+)	6.38 ± 1.35	0.79 ± 0.61
CALR (+)	5.80 ± 0.87	2.45 ± 5.24
MPLW515L (+)	6.26 ± 0.00	0.58 ± 0.00
Triple-negative	5.37 ± 0.94	0.58 ± 0.11
prePMF	5.65 ± 0.84	0.71 ± 0.47
JAK2V617F (+)	5.68 ± 0.92	0.64 ± 0.21
CALR (+)	5.89 ± 0.96	0.91 ± 0.82
MPLW515L (+)	-	-
Triple-negative	5.10 ± 0.32	0.54 ± 0.05
fibrotic PMF	6.25 ± 1.30	1.66 ± 3.82
JAK2V617F (+)	6.54 ± 1.40	0.89 ± 0.78
CALR (+)	5.76 ± 0.90	3.67 ± 7.08
MPLW515L (+)	6.26 ± 0.00	0.58 ± 0.00
Triple-negative	5.51 ± 1.17	0.62 ± 0.17

Legend: TAC—total antioxidant capacity, 8-OHdG—8-hydroxy-2′-deoxy-guanosine, MPNs—myeloproliferative neoplasms, sAML—secondary acute myeloid leukemia, PV—polycythemia vera, ET—essential thrombocythemia, MF—myelofibrosis, prePMF—prefibrotic primary myelofibrosis, and PMF—primary myelofibrosis.

As compared to the literature, Genovese et al. have reported elevated TAC in PMF, signaling associations between TAC and bone marrow fibrosis, DIPSS scores, and the number of circulating CD34-positive cells (Genovese, 2022). Moreover, both in *de novo* AML and sAML, the genetic landscape can shape cell signaling phenomena involved in OS generation which, in turn, can exert, *via* elevated reactive oxygen species concentrations, positive selection pressure on leukemic stem cells and eventually drive clonal evolution and AML development (Chen, 2022; Chen, 2023a; Chen, 2023b; Robinson, 2021).

Moreover, within this chapter, we presented the results of a qualitative assessment of 27 original studies, as the results of a systematic review of the literature regarding the role of liquid biopsy in MPNs. This novel technique can be used to quantify several biomarkers (cell-free

DNA, extracellular vesicles, microparticle, circulating endothelial cells) with a potential diagnostic and prognostic purpose in MPNs.

Chapter 7, entitled ***„Study no. 2: QoL evaluation in classical BCR::ABL1-negative MPNs: translation, cultural adaptation and validation to Romanian of the MPN-10 (MPN-SAF TSS) questionnaire for symptom burden assessment”,*** summarizes the results of a clinical investigation in which we translated, culturally adapted and validated to Romanian the MPN-10 questionnaire used to quantify symptom burden and QoL in MPNs (Găman, 2024b).

The research was carried out in the Department of Hematology, Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, and the Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Bucharest, Romania. The study was approved by the local ethics committees/councils of both institutions (approval no. 40542/07.06.2021, approved on 27.05.2021; and approval no. 3982/13.04.2021, approved on 13.04.2021, respectively) and was conducted between June 2021 and December 2023.

MPN-10 consists of 10 items, the first (worst fatigue) derived from the „Brief Fatigue Inventory” and nine others (early satiety, abdominal pain, inactivity, concentration problems, night sweats, itching, bone pain, involuntary weight loss in the last six months and fever >37.7 Celsius degrees), and was conceived based on the most frequently reported symptoms by MPN patients. Subjects rate each item on a scale from 0 points (the symptom is absent) to 10 points (the symptom is as bad as it can be), and the final score (total symptom score, TSS) results from the sum of the ratings of each symptom. Patients were invited to complete the survey during their visits to the outpatient clinic or when they were hospitalized in the clinical ward.

The translation, cultural adaptation, and validation of the MPN-10 were carried out in agreement with international guidelines. The sample size was calculated based on the PRO guidelines at a minimum of 80-100 subjects: 8-10 responses/each item of MPN-10, thus 8-10 responses/item x 10 items = 80-100 participants. Statistical analysis was carried out in JASP version 0.18.3.0.

Regarding **the results of study no. 2**, the study group consisted of 180 MPN cases: PV (36.67%; n = 66), ET (33.89%; n = 61), MF (28.33%; n = 51), and MPN unclassifiable (MPNu) (1.11%; n = 2). MF patients (n = 51) had either PMF (n = 34) or post-PV SMF (n = 7) or post-ET SMF (n = 10). The mean age of the enrolled patients was 62.75 ± 12.36 years, and 54.44%

were female. *JAK2V617F* mutation was detected in 141 MPN cases (78.33%), whereas *CALR* type 1 or 2 mutations were noted in 10 cases (5.55%).

For the entire MPN cohort, TSS was calculated at 19.51 ± 16.51 points. TSS was higher in MF (24.84 ± 19.63 points) versus PV (18.95 ± 14.38 points) or ET (15.30 ± 14.88 points). TSS was elevated in post-PV (29.86 ± 15.39 points) and post-ET (24.50 ± 27.39 points) SMF versus PMF (23.91 ± 18.16 points). MPNu had the highest TSS (30.50 ± 3.54 points), however, we enrolled only two patients with MPNu.

Symptom burden was highest for fatigue (3.67 ± 2.77 points), inactivity (2.73 ± 2.71 points) and concentration problems (2.39 ± 2.55 points) for the entire MPN cohort. Symptom burden and QoL assessment in our MPN cohort is listed in **Table 4.** Symptom burden and QoL assessment in MF patients is reported in **Table 5**.

Table 4. Symptom burden and QoL assessment in the entire MPN cohort

Symptom	**PV (*n* = 66)**			**ET (*n* = 61)**			**MF (*n* = 51)**			**MPNs (total) (*n* = 180)**			***p-value***
	Mean	**SD**	**Incidence**	**Mean**	**SD**	**Incidence**	**Mean**	**SD**	**Incidence**	**Mean**	**SD**	**Incidence**	
Worst fatigue	3.73	2.64	92.42%	2.80	2.52	86.89%	4.51	2.96	86.27%	3.67	2.77	88.89%	$p = 0.004$; MF vs. TE, $p = 0.002$
Early satiety	1.23	1.80	48.49%	1.61	2.42	52.46%	2.75	2.84	70.59%	1.84	2.45	56.67%	$p = 0.002$; MF vs. PV, $p = 0.001$; MF vs. TE, $p = 0.02$
Abdominal pain	1.20	1.90	48.49%	1.23	2.12	40.98%	2.12	2.81	58.82%	1.49	2.32	48.89%	$p = 0.057$
Inactivity	2.74	2.49	78.79%	2.16	2.35	68.85%	3.18	3.12	72.55%	2.73	2.71	73.89%	$p = 0.128$
Concentration problems	2.52	2.43	71.21%	2.16	2.36	63.93%	2.55	2.93	66.67%	2.39	2.55	67.22%	$p = 0.663$
Night sweats	2.68	2.92	72.73%	1.43	2.65	44.26%	2.82	3.24	64.71%	2.27	2.97	60.56%	$p = 0.018$; MF vs. TE, $p = 0.029$
Itching (pruritus)	2.11	2.55	66.67%	0.93	2.23	22.95%	1.49	2.37	43.14%	1.51	2.42	44.44%	$p = 0.024$; PV vs. TE, $p = 0.023$
Bone pain	1.77	2.49	60.61%	2.16	2.88	57.38%	2.86	3.40	66.67%	2.19	2.92	60.56%	$p = 0.133$
Fever (>37.7 Celsius)	0.28	1.44	6.06%	0.05	0.28	3.28%	0.35	1.28	9.80%	0.22	1.12	6.11%	$p = 0.321$
Unintentional weight loss in the last 6 months	0.72	1.32	34.85%	0.75	1.70	31.15%	2.27	3.23	52.94%	1.22	2.28	39.44%	$p < 0.001$; MF vs. PV, $p < 0.001$; MF vs. TE, $p < 0.001$
QoL	7.39	1.39		7.61	1.79		7.25	2.27		7.44	1.81		$p = 0.584$

TSS	18.95	14.38		15.30	14.88		24.84	19.63		19.51	16.51		$p = 0.008$; MF vs. TE, $p = 0.004$

Legend: QoL, quality of life. TSS, total symptom score. PV, polycythemia vera. ET, essential thrombocythemia. MF, myelofibrosis. PMF, primary myelofibrosis. n, number. SD, standard deviation.

Table 5. Symptom burden and QoL assessment in MF patients

Symptom	**PMF (*n* = 34)**			**post-ET SMF (*n* = 10)**			**post-PV SMF (*n* = 7)**			**MF (total) (*n* = 51)**			***p-value***
	Mean	**SD**	**Incidence**	**Mean**	**SD**	**Incidence**	**Mean**	**SD**	**Incidence**	**Mean**	**SD**	**Incidence**	
Worst fatigue	4.18	2.81	85.29%	5.10	3.75	80.00%	5.29	2.50	100.00%	4.51	2.96	86.27%	$p = 0.527$
Early satiety	2.79	2.73	76.47%	2.00	3.09	40.00%	3.57	3.21	85.71%	2.75	2.84	70.59%	$p = 0.534$
Abdominal pain	2.06	2.78	58.82%	2.30	3.77	40.00%	2.14	1.35	85.71%	2.12	2.81	58.82%	$p = 0.972$
Inactivity	2.76	2.77	70.59%	3.90	4.36	60.00%	4.14	2.73	100.00%	3.18	3.12	72.55%	$p = 0.415$
Concentration problems	2.44	2.85	64.71%	2.40	3.37	60.00%	3.29	3.04	85.71%	2.55	2.93	66.67%	$p = 0.780$
Night sweats	2.85	3.22	61.76%	2.50	3.57	50.00%	3.14	3.34	100.00%	2.82	3.24	64.71%	$p = 0.921$
Itching (pruritus)	1.59	2.63	41.18%	1.50	1.84	50.00%	1.00	1.83	42.86%	1.49	2.37	43.14%	$p = 0.841$
Bone pain	2.50	3.28	61.76%	3.10	4.12	70.00%	4.29	2.93	85.71%	2.86	3.40	66.67%	$p = 0.444$
Fever (>37.7 Celsius)	0.35	1.32	8.82%	0.50	1.58	10.00%	0.14	0.38	14.29%	0.35	1.28	9.80%	$p = 0.856$
Unintentional weight loss in the last 6 months	2.47	3.40	55.88%	1.20	2.53	30.00%	2.86	3.39	71.43%	2.27	3.23	52.94%	$p = 0.491$
QoL	7.47	2.08		7.00	3.13		6.57	1.90		7.25	2.27		$p = 0.595$
TSS	23.91	18.16		24.50	27.39		29.86	15.39		24.84	19.63		$p = 0.771$

Legend: QoL, quality of life. TSS, total symptom score. PV, polycythemia vera. ET, essential thrombocythemia. MF, myelofibrosis. PMF, primary myelofibrosis. n, number. SD, standard deviation.

We demonstrated significant differences between MPN subtypes in terms of TSS ($p = 0.021$) and individual scores for: weight loss ($p < 0.001$; PMF vs. PV, $p = 0.001$; PMF vs. ET, $p = 0.002$), worst fatigue ($p = 0.006$; SMF vs. ET, $p = 0.009$), early satiety ($p = 0.007$; PMF vs. PV, $p = 0.011$), night sweats ($p = 0.047$), and itching ($p = 0.05$). Moreover, we detected strong positive associations between TSS and inactivity ($r = 0.741$, $p < 0.001$), worst fatigue ($r = 0.734$, $p < 0.001$), and concentration problems ($r = 0.709$; $p < 0.001$). Moreover, we noted negative correlations between QoL scores and all items of the Romanian version of the MPN-10 (RO-MPN-10)($p < 0.001$). **Figure 4** depicts the identified correlations between RO-MPN-10 items.

Internal consistency of RO-MPN-10 was excellent (Cronbach α coefficient = 0.855; **Table 6**), ranging from 0.830 (itching) and 0.861 (fever). Construct validity (Kaiser-Meyer-Olkin test = 0.870, **Table 7**; Bartlett sphericity test: $X^2 = 616.968$, df = 45, $p < 0.001$) was also solid.

Exploratory factor analysis revealed that all symptoms loaded into a single factor (**Table 8; Figure 5**). The test-retest procedure was carried out in 63 MPN cases and highlighted that RO-MPN-10 scores did not change significantly between visits (p = 0.24), however, it was able to detect changes in disease biology, i.e., TSS increased and QoL decreased in subjects who progressed to SMF or sAML.

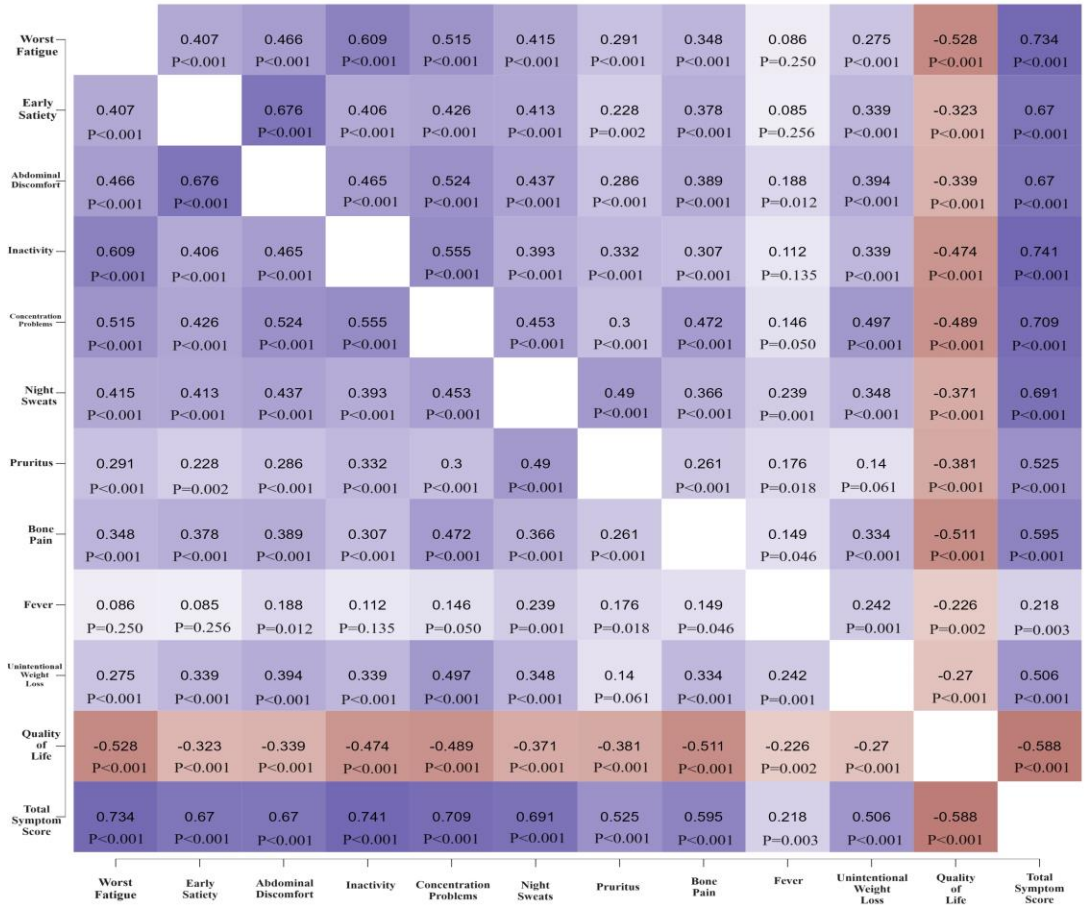


Figure 4. Correlation matrix between RO-MPN-10 items

Legend: QoL, quality of life. TSS, total symptom score**.**
(Source: original figure – see Găman et al., 2024b)

Table 6. Cronbach α coefficients for RO-MPN-10 items

Item	Cronbach α coefficient	95% CI
Worst fatigue	0.838	0.807, 0.871
Early satiety	0.837	0.802, 0.867
Abdominal pain	0.833	0.798, 0.865
Inactivity	0.841	0.812, 0.875
Concentration problems	0.832	0.797, 0.865
Night sweats	0.832	0.797, 0.865

Itching (pruritus)	0.831	0.797, 0.865
Bone pain	0.842	0.811, 0.875
Fever	0.861	0.831, 0.890
Weight loss	0.845	0.814, 0.876

Legend: CI, confidence interval

Table 7. Kaiser-Meyer-Olkin test results for RO-MPN-10 items

Item	MSA
Worst fatigue	0.870
Early satiety	0.866
Abdominal pain	0.859
Inactivity	0.884
Concentration problems	0.843
Night sweats	0.865
Itching (pruritus)	0.896
Bone pain	0.863
Fever	0.910
Weight loss	0.759

Legend: MSA, the measure of sampling adequacy

Table 8. Exploratory factor analysis results for RO-MPN-10

Factor	Eigenvalue (real)	Eigenvalue (simulated)
Factor 1*	4.418	1.392
Factor 2	1.014	1.261
Factor 3	0.912	1.175
Factor 4	0.851	1.096
Factor 5	0.665	1.028
Factor 6	0.611	0.960
Factor 7	0.429	0.888
Factor 8	0.410	0.811
Factor 9	0.373	0.722
Factor 10	0.317	0.666

Moreover, since MPN-10 was frequently used in randomized clinical trials to assess treatment impact on constitutional symptoms in MPNs, this chapter also tackled the subjects of JAK1/2 inhibition in MPNs and listed several of the non-hematological side effects of JAK inhibitors, e.g., liver toxicity and the risk of opportunistic infections or reactivation of latent infections (Purwar, 2023; Adesola, 2023).

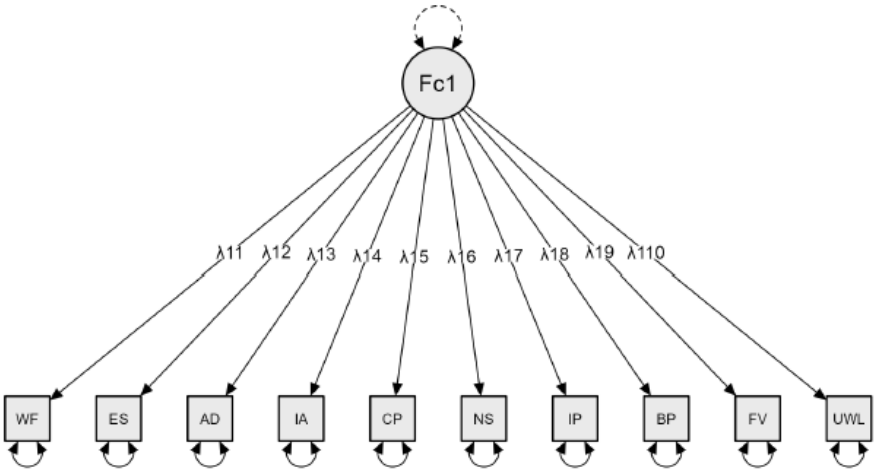


Figure 5. Factor loading in RO-MPN-10. (Source: original figure).
Legend: WF, worst fatigue. ES, early satiety. AD, abdominal discomfort. CP, concentration problems. NS, night sweats. IP, itching/pruritus. BP, bone pain. FV, fever. UWL, unintentional weight loss.

Chapter 8, entitled ***„Study no. 3 – Cardiovascular risk factors and classical BCR::ABL1-negative MPNs”***, gives insight into cardio-oncology, assessing the impact of CVRF on thrombotic risk in MPNs. What is more, we summarized the available literature data on less analyzed CVRF, such as dyslipidemia and metabolic syndrome (**Figure 6**) or T2DM, as well as on two thrombotic events occurring in MPNs: acute myocardial infarction (**Figure 7**) and Budd-Chiari syndrome. Moreover, we established a diagnostic algorithm for Budd-Chiari syndrome related to MPNs (Găman, 2024c; Manan, 2023; Găman, 2023b).

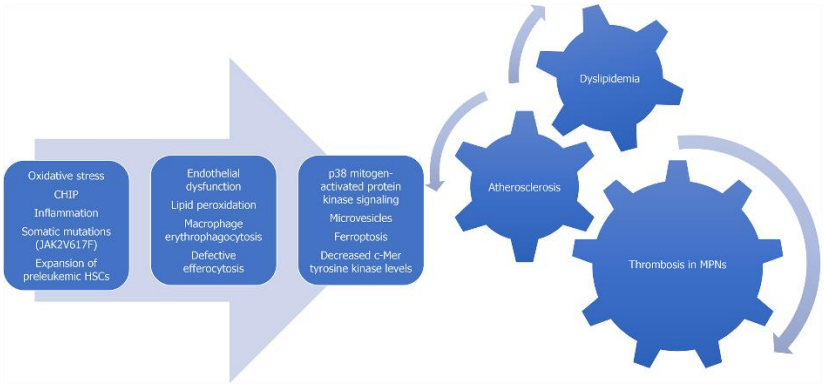
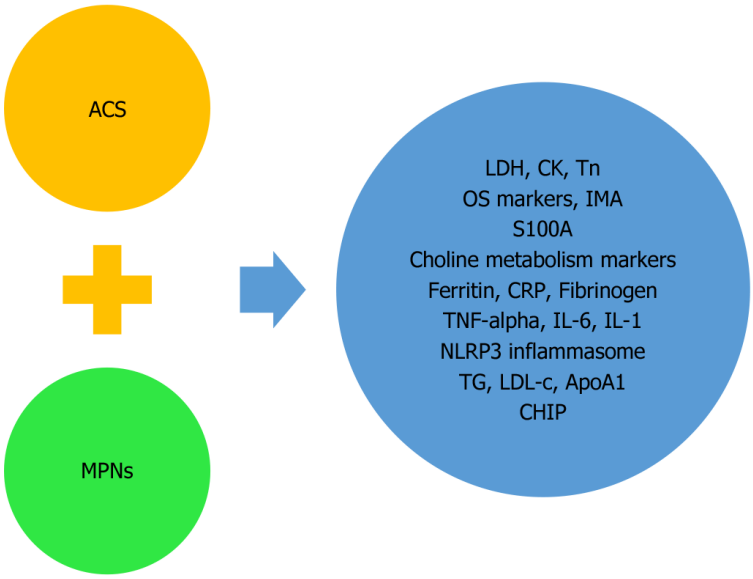


Figure 6. Schematic representation of the interplay among dyslipidemia, atherosclerosis, and MPNs**.** (Source: original figure – see Găman, 2024c)

In addition, we reported the results of a systematic review of the literature which included 74 publications in which we evaluated the interplay between HTN and MPNs, the impact of HTN on thrombotic risk in MPNs, treatment options for MPN patients who suffer from HTN, as well as data on drug-induced HTN caused by MPN therapeutic agents (Găman, 2023a).



DOI: 10.4330/wjc.v15.i11.571

Figure 7. Potential common biomarkers for MPNs and acute coronary syndromes.

(Source: original figure – see Manan M, Kipkorir V, ..., Diaconu CC, **Găman MA**, 2023)

Legend: MPNs: Myeloproliferative neoplasms; ACS: Acute coronary syndromes; LDH: Lactate dehydrogenase; CK: Creatine kinase; Tn: Troponin; OS: Oxidative stress; IMA: Ischemia-modified albumin; CRP: C-reactive protein; TNF-alpha: Tumor necrosis factor alpha; IL-6: Interleukin-6; IL-1: Interleukin-1; TG: Triglycerides; LDL-c: Low-density lipoprotein cholesterol; ApoA1: Apolipoprotein A1; CHIP: Clonal hematopoiesis of indeterminate potential.

Moreover, this chapter also reported the results of a retrospective cohort study of over 150 ET patients in whom we evaluated the presence of CVRF and their impact on thrombosis. Of these patients, more than 30% experienced thrombotic complications many of which were inaugural events in MPN diagnosis. Male sex, several symptoms, e.g., abdominal discomfort, chronic liver disease, or leukocytosis were associated with major thrombotic events in ET. The death rate was elevated in ET patients with a history of major thrombosis (RR = 2.66; 95% CI 1.24-5.70, P=0.02), however, survival was only influenced by age and *JAK2V617F* status, with *JAK2V617F*-positive ET patients older than 60 years displaying the lowest survival rates (Pîrciulescu, 2022).

Chapter 9 overviews the original contributions of this PhD thesis to the state of knowledge and present future perspectives of the doctoral research. My PhD thesis puts forth

several original concepts: we evaluated for the first time OS in MPNs versus sAML and healthy controls, we investigated the OS – genetic landscape interplay in MPNs and sAML, as well as symptom burden and QoL in Romanian MPN patients, we conducted the translation, cultural adaptation and validation to Romanian of the MPN-10 and tested its psychometric properties, we proposed liquid biopsy as an emerging non-invasive technique to assess MPNs and quantify novel biomarkers (cell-free DNA, extracellular vesicles, microparticle, circulating endothelial cells), we analyzed the impact of less studied CVRF (dyslipidemia, metabolic syndrome, T2DM) on thrombosis in MPNs. Limitations of the current research include the fact that we were not able to assess OS from samples other than plasma, as well as the impact of the COVID-19 pandemic on patients' addressability to the hospital which reduced enrolment rates. However, I believe that the originality of my PhD thesis, which combined experimental research with clinical investigations and theoretical research, reviving the concept of "from bench to bedside", as well as its interdisciplinary vision, surpasses the limitations of my doctoral project. Moreover, the PhD thesis is valuable also because the results of the theoretical and practical findings were published in 15 publications for which I was the main author (three original research papers, two systematic reviews, eight narrative reviews, and two editorials). During the near future, I envision that I will extend my current research by evaluating other OS markers in MPNs and sAML, as well as by conducting a prospective multicentric study to investigate QoL in MPNs.

Chapter 10 provides the conclusions of PhD thesis:

1. Our study reinforces the involvement of OS in MPN pathogenesis, the measurement of TAC and 8-OHdG in these hematological malignancies demonstrating elevated TAC ($p = 0.03$) and similar 8-OHdG levels in MPNs versus sAML and healthy controls.
2. My doctoral research depicts a significant association between TAC and MPNs ($OR = 1.82$; $p = 0.05$), with patients with elevated TAC displaying a nearly two times higher risk of MPNs.
3. ET and PMF subjects expressed higher TAC versus PV, sAML, and controls. In ET, TAC was notably higher in the presence of the *MPLW515L* mutation.
4. Patients with fibrotic PMF who had previously received treatment had lower TAC ($p = 0.03$) versus treatment-naïve PMF subjects.

5. Concentrations of 8-OHdG were similar between controls, MPNs, and sAML, most probably because this OS marker was evaluated from plasma and not urine samples.
6. The genetic landscape in MPNs was dominated by the *JAK2V617F* mutation (>70% of cases), followed by *CALR* (18% of cases) and *MPLW515L* mutations (<5% of cases), whereas less than 5% of patients were triple-negative for driver mutations in the *JAK2*, *CALR*, and *MPL* genes.
7. More than a half of sAML cases harbored the *JAK2V617F* mutation, over a quarter were triple-negative and one fifth were *CALR*-positive. Most frequent sAML cases encountered in our study were secondary to PMF.
8. In terms of additional non-driver mutations, although NGS data was only available for sAML cases, we observed elevated TAC levels in patients in whom somatic driver gene mutations were associated with additional mutations in genes such as *ASXL1*, *FLT3*, *TET2*, *IDH2* or *STAG2*.
9. In terms of QoL and symptom burden in MPNs, we demonstrated a significant reduction in QoL of approximately 30% in Romanian patients with MPNs, as well as a high disease burden with a mean TSS of approximately 20 points.
10. Symptom burden was highest in MF (TSS ≅ 25 points), followed by PV (TSS ≅ 19 points) and ET (TSS ≅ 15 points). In particular, post-PV SMF (TSS ≅ 30 points) and post-ET (TSS ≅ 25 points) SMF patients exhibited higher symptom burden versus PMF (TSS ≅ 24 points), PV or ET cases.
11. Fatigue, inactivity, and concentration problems were the most cumbersome symptoms in our MPN cohort.
12. Unintentional weight loss was a frequently reported symptom in MPNs ($p < 0.001$), with patients with PMF ranking it higher on the TSS scale versus those with PV ($p = 0.001$) or ET ($p = 0.002$).
13. Fatigue score were different between MPN subtypes ($p = 0.006$), particularly between SMF and ET ($p = 0.006$), fatigue being a more severe symptom in the former.
14. We discovered notable differences between MPN subtypes in terms of early satiety ($p = 0.007$), the patients with PMF ($p = 0.011$) ranking this symptom higher on the TSS scale versus PV subjects. TSS ($p = 0.021$), as well as individual scores for night sweats ($p = 0.047$) and itching ($p = 0.05$), were also significantly different between MPN subtypes.

15. Our data suggests correlations between MPN symptoms. We highlighted positive associations between TSS and inactivity ($r = 0.741$, $p < 0.001$), fatigue ($r = 0.734$, $p < 0.001$), and concentration problems ($r = 0.709$; $p < 0.001$). Moreover, QoL scores were negatively and moderately correlated with MPN symptoms in our cohort.
16. The Romanian version of the MPN-10 displayed excellent psychometric properties. Internal consistency was excellent, with a Cronbach α coefficient of 0.855, ranging from 0.830 for itching to 0.861 for fever. Construct validity was solid (Kaiser-Meyer-Olkin test = 0.870, Bartlett sphericity test $p < 0.001$). Exploratory factor analysis revealed that all items were loaded into one single factor. Test-retest method highlighted that TSS did not change significantly between patient visits, with the exception of subjects who progressed to SMF or sAML, suggesting that RO-MPN-10 exhibits discriminatory potential.
17. In terms of liquid biopsy applications in MPNs, our qualitative analysis reveals that this technique might be useful in these hematological malignancies, particularly to quantify several biomarkers (cell-free DNA, extracellular vesicles, microparticle, circulating endothelial cells) with a potential diagnostic and prognostic purpose in MPNs.
18. Regarding the CVRF – MPNs interplay, the results of our research suggest that HTN is the most common comorbidity in MPNs, with a negative impact on thrombotic risk, survival and treatment strategies. The association of HTN and MPNs implies, apart from an elevated thrombotic rate, the development of end-organ damage and, due to increased blood viscosity, a limitation of HTN therapeutic lines by the removal of diuretics from the treatment options. T2DM, dyslipidemia and metabolic syndrome exhibit similar effects on thrombotic risk and survival in MPNs.
19. Our unicentric experience in ET diagnosis and management highlights an elevated frequency of CVRF and thrombotic events in this MPN subtype, with over a third of patients experiencing arterial, venous or mixed thromboses.
20. Although ET patients with a history of major thrombosis had lower survival rates, only advances age, over 60 years, and the presence of the *JAK2V617F* mutation had a decisive impact on death rates.

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List of publications

Full-text articles published as the main author in Clarivate Analytics-indexed journal (impact factor journals)(first, last or corresponding author)

1. **Găman MA**, Mambet C, Neagu AI, Bleotu C, Gurban P, Necula L, Botezatu A, Ataman M, Diaconu CC, Ionescu BO, Ghiaur AE, Tatic A, Coriu D, Găman AM, Diaconu CC. Assessment of Total Antioxidant Capacity, 8-Hydroxy-2'-deoxy-guanosine, the Genetic Landscape, and Their Associations in *BCR::ABL-1*-Negative Chronic and Blast Phase Myeloproliferative Neoplasms. **Int J Mol Sci**. 2024 Jun 17;25(12):6652. doi: 10.3390/ijms25126652. PMID: 38928358; PMCID: PMC11203765.
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13. **Găman MA**, Cozma MA, Dobrică EC, Crețoiu SM, Găman AM, Diaconu CC. Liquid Biopsy and Potential Liquid Biopsy-Based Biomarkers in Philadelphia-Negative Classical Myeloproliferative Neoplasms: A Systematic Review. Life (Basel). 2021 Jul 10;11(7):677. doi: 10.3390/life11070677. PMID: 34357048; PMCID: PMC8304270.
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Book chapter

1. **Găman MA,** Diaconu CC. Capitolul 52: Policitemia vera şi trombocitemia esenţială. Tratat de Medicină Internă: pg. 810-815. Editura "ALL", Bucureşti, 2024, sub redacţia Prof. Univ. Dr. Camelia Cristina Diaconu. ISBN: 978-606-587-623-1.
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Meeting abstracts at international/national congresses/conferences

1. **Găman MA**, Scherber RM, Ursuleac I, Crişan AM, Bădeliţă SN, Ionescu BO, Ghiaur AE, Brînză M, Pîrciulescu N, Lascăr TO, Diaconu CC, Găman AM, Coriu D. P2296. Assessment of Health-related Quality of Life in Romanian patients with *BCR::ABL1*-negative myeloproliferative neoplasms: first report. Hemasphere. 2024;8(S1): 4345-4346. Impact Factor: 12.1. **E-poster**, EHA2024 Congress, 13-16 June, Madrid, Spain.
2. **Găman MA.** PB2227: Transformation of myeloproliferative neoplasms into acute promyelocytic leukemia: systematic review and meta-analysis of case reports. HemaSphere 7(S3):p.e02896a8. Meeting abstract accepted at the EHA2023 Congress.
3. **Găman MA.** PB2242: Acute lymphoblastic leukemia secondary to essential thrombocythemia: systematic review and meta-analysis of case reports**.** HemaSphere 7(S3):p.e0420978. Meeting abstract accepted at the EHA2023 Congress.
4. **Găman MA**, Găman AM, Diaconu CC. Drug-Induced Hypertension in Classical Philadelphia-Negative Myeloproliferative Neoplasms (MPNs): Systematic Review. Clin Lymphoma Myeloma Leuk. 2022;(2022):S323-S323. Poster, **abstract awarded with a Travel Grant from SOHO**.
5. **Găman MA.** P1025 Ruxolitinib-Associated Cryptococcosis: A Systematic Review and Meta-Analysis. HemaSphere, 2022;6:(S3):915-916 doi: 10.1097/01.HS9.0000846968.59379.66. Impact Factor (2021): 8.300. Poster, EHA Congress 2022, 9-12 June 2022, Vienna, Austria – **abstract awarded with a Travel Grant from EHA**
6. **Găman MA,** Găman AM, Diaconu CC. PB2053 Primary Arterial Hypertension in Myeloproliferative Neoplasms: A Systematic Review. HemaSphere, 2022;6:(S3):1924-1925. doi: 10.1097/01.HS9.0000851044.26885.b9. Impact Factor (2021): 8.300. Meeting abstract accepted at the EHA2022 Congress.
7. **Găman MA,** Epîngeac ME, Găman AM, Diaconu CC. Obesity and Myeloproliferative Neoplasms: A Systematic Review. J Hypertens. 2022;40(Suppl 1):e121-e121. doi: 10.1097/01.hjh.0000836480.33984.57. Impact Factor: 4.766. E-poster, Cardiovascular Oncology section, 31st European Meeting on Hypertension and Cardiovascular Protection.
8. **Găman MA**, Găman AM, Diaconu CC. Targeted Anticancer Therapy - a Cause of Drug-Induced Hypertension in Myeloproliferative Neoplasms: Systematic Review. E-poster, European School of Hematology (ESH) 9th Translational Research E-Conference on MYELOPROLIFERATIVE NEOPLASMS. May 12-15, 2022.
9. Coriu D, Dobrea C, Tatic A, Crisan M, **Găman M**, Mihailescu M, Constantin C, Dragomir M, Mambet C, Ursuleac I. Clin Chem Lab Med. 2021 Oct 21;59(s1):s80-s93. doi: 10.1515/cclm-2021-5002. PMID: 34727600. Impact Factor: 8.490. – Oral presentation, 24th

IFCC-EFLM European Congress of Clinical Chemistry and Laboratory Medicine - National Congress of the German Society of Laboratory Medicine.

10. **Găman MA**, Cozma MA, Dobrică EC, Crețoiu SM, Găman AM, Diaconu CC. Potential Applications of Liquid Biopsy in BCR-ABL1-Negative Myeloproliferative Neoplasms: A Systematic Review. Clin Lymphoma Myeloma Leuk. 2021;21(Suppl 1):S364-S365. Impact Factor (2020): 3.231. E-Poster Presentation MPN-369, Proceedings of the Society of Hematologic Oncology 2021 Annual Meeting, Ninth Annual (Virtual) Meeting, September 8–11, 2021, United States – **abstract awarded with a Travel Grant from SOHO**.
11. **Găman MA**, Găman AM, Diaconu CC. Heart Failure: A Cause of Polypharmacy, Drug-Drug, and Food-Drug Interactions in Essential Thrombocythemia. Clin Lymphoma Myeloma Leuk. 2021;21(Suppl 1):S352-S352. Impact Factor (2020): 3.231. E-Poster Presentation MPN-028, Proceedings of the Society of Hematologic Oncology 2021 Annual Meeting, Ninth Annual (Virtual) Meeting, September 8–11, 2021, United States - **abstract awarded with a Travel Grant from SOHO**
12. **Găman MA**, Găman AM, Diaconu CC. Anxiety, Depression and Insomnia in Myeloproliferative Neoplasms: a Systematic Review. Maedica. 2021 (Suppl): in press. E-poster presentation, The Congress of the "Carol Davila" University of Medicine and Pharmacy, 25-27 November 2021, Bucharest.
13. **Găman MA**, Cozma MA, Dobrica EC, Cretoiu SM, Gaman AM, Diaconu CC. Novel strategies of evaluation and management in myeloproliferative neoplasms. Arch Balk Med Union. 2021;56(Suppl 1):S42-S42. Oral presentation, The 23rd BALKAN MEDICAL DAYS: Balkan Medicine during the COVID-19 pandemic, 1-2 October 2021.
14. Găman MA, Coriu D, Ursuleac I. Ruxolitinib-associated tuberculosis in myeloproliferative neoplasms (MPN): systematic review and meta-analysis of 26 case reports. HemaSphere. 2021;5(S2):535-536. E-poster presentation, EHA2021 Congress – **abstract awarded with a Travel Grant from EHA**