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– ORIGINAL PAPER –

A Single Center's Experience in the Diagnosis and Treatment of Myeloproliferative Neoplasms

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Abstract

Introduction: *Philadelphia-negative myeloproliferative neoplasms (MPN) represent a polymorphous group of hematopoietic disorders that have been intensely studied from a clinical, molecular, and histopathological point of view. Recent updates to classification and diagnosis criteria have increased the rate of identification, particularly among patients who were previously underdiagnosed.*

Methods: *We report the results of Colțea Clinical Hospital's experience in diagnosing and treating newly diagnosed PV, ET, PMF, and MPN-U between January 2022 and September 2024, including 154 patients over the age of 18.*

Results: *Out of the 154 cases analysed, 31.82% were diagnosed with PV (N = 49), 31.82% with essential thrombocythemia (ET; N = 49), and 30.52% with MF (N = 47). Additionally, 5.84% (N = 9) presented as unclassifiable (MPN-U). Out of the enrolled patients, 87 (56.49%) had associated cardiovascular risk factors, 33 (21.43%) had a history of thrombosis at diagnosis, while 7 (4.55%) patients presented at least one hemorrhagic event, most notably gastrointestinal. Risk stratification for PV, ET, and PMF was calculated according to the ELN recommendations for PV, the IPSET score, and the IPSS/DIPSS, respectively. A significant group, 128 (83.12%), required therapeutic intervention.*

Conclusion: *MPNs can cause significant morbidity in the form of burdensome symptoms, potentially fatal cardiovascular complications or progression to acute myeloid leukaemia. The higher rate of diagnosis and the emergence of novel therapies in recent years have prolonged life expectancy and improved the quality of life.*

Keywords: *Myeloproliferative neoplasms; Philadelphia negative; Diagnosis; Treatment options*

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Introduction

Philadelphia-negative chronic myeloproliferative neoplasms (MPN) represent clonal hematopoietic stem cell diseases characterised by overproduction of at least one myeloid blood lineage associated with effective hematopoiesis and maturation, primarily affecting elderly patients. (1)(2) Primary myelofibrosis presents with bone marrow fibrosis, extramedullary hematopoiesis and splenomegaly. Tumour progression and disease severity are related to the chronic inflammatory status of the medullary environment. (3)

The World Health Organization (WHO) 2016 Classification includes BCR::ABL1 negative polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), MPN, unclassifiable (MPN-U), and the myeloleukaemia syndromes, such as chronic neutrophilic leukaemia and chronic eosinophilic leukaemia.(4)(5) The revised 2022 WHO-HAEM5 Classification includes juvenile myelomonocytic leukemia (JMML) amongst other BCR::ABL1-negative MPN, and encompasses the heterogeneous MPN-U as myeloproliferative neoplasm, not otherwise specified (MPN-NOS)(6), while the International Consensus Classification 2022 recognises the WHO 2016 terminology for MPN-U.(4)

This study focuses on the classic myeloproliferative syndromes: PV, ET, and PMF, considering the pre-fibrotic and overt fibrotic stages separately. It also includes MPN-U, which presents with myelofibrosis in the absence of myelodysplastic features, as observed on bone marrow biopsy.

According to the 2022 WHO guidelines, bone marrow histology has become a major criterion for diagnosis, aiming to avoid underdiagnosing MPNs, differentiate between PV, ET, and pre-PMF, and decrease the rate of unclassifiable cases.(4)(7) MPN-U was defined as a distinct entity presenting some clinical or morphological characteristics of MPN, associated with a mutated JAK2, CALR, MPL, or another clonal marker. Typically, these are MPNs diagnosed in the early fibrotic or advanced fibrotic phase, or MPNs associated with inflammatory or neoplastic disorders that can mask the diagnosis. (5)(8)

Molecular profiling enables the prediction of prognosis and guides further therapeutic decisions. 85% of patients present with mutually exclusive JAK2, CALR, and MPL mutations that activate the JAK-STAT pathway. The JAK2V617F driver lesion is most commonly associated with PV, ET, and MF, with a detection rate in PV of up to 96%. (2)(9) However, a small number of patients lack JAK-STAT driver mutations, which is considered “triple-negative.”(10) All causes of high blood cell counts should be excluded, while a bone marrow biopsy should confirm the MPN diagnosis.(8) BCR::ABL1 rearrangement should also be excluded in these cases. Next-generation Sequencing (NGS) may be the next step in molecular diagnosis, with recent data indicating that mutations in TP53, ASXL1, SF3B1, SRSF2, and U2AF1 may specifically indicate primary myelofibrosis (PMF). Furthermore, mutations in JAK2 Exon 12 or a homozygous JAK2 relate to PV. (11) TP53 mutations present an increased risk of transformation to AML; additionally, IDH1/2 mutations predispose to post-MPN AML. (1)

MPNs are associated with a substantial risk for venous thromboembolism, arterial thrombosis and bleeding. (12) Prior thrombosis, age over 60 years, cardiovascular comorbidities, and the presence of TET2 or DNMT3A mutations were identified as risk factors for arterial thrombosis in the ARTS (ARterial Thrombosis Score). In contrast, the presence of the JA2V617F mutation with a variable allele frequency (VAF) over 50% and a prior thrombotic event were associated with a higher risk of venous thrombosis. (13)

Hemorrhagic events are more frequent in ET, especially in cases of extreme thrombocytosis. The leading cause of bleeding is an acquired von Willebrand syndrome (vVWS), through either ADAMTS-13-regulated increased proteolysis or increased absorption of vWF by the high number of platelets (14). Microvascular complications can also be observed. (15)

According to the International Prognostic Score for Essential Thrombocythemia (IPSET), age at diagnosis over 60 years, cardiovascular comorbidities, and significant thrombocytosis (platelet count over 1,500 x 10^9/L) are risk factors to consider when initiating cytoreductive treatment in ET. Age ≥ 60 years and a history of thrombosis also represent a treatment indication in PV. Prognostic models for PMF include age ≥ 65 years, the presence of constitutional symptoms, haemoglobin < 10 g/dL, WBC count > 25 × 10^9/L, and the level of circulating blasts according to the International Prognostic Scoring System (IPSS). The later developed Dynamic International Prognostic Scoring System (DIPSS) includes unfavourable karyotype, PLT count under 100 x 109 /L and transfusion requirement. (16)

The only curative option for myelofibrosis-diagnosed patients is allogeneic hematopoietic stem cell transplantation. (2) Transplant-related mortality and

morbidity, especially in the context of a median age at diagnosis of 60 years, limit the use of allo-HCT. Recent developments in conditioning therapy, HLA donor selection and GVHD management have led, however, to more extensive transplant indications for elderly patients. (17) (18)

Janus-activated kinase (JAK) inhibitors are currently the standard of care for intermediate- to high-risk myelofibrosis and patients with refractory or resistant polycythemia vera (PV). (19)

Ruxolitinib has been reported to improve constitutional symptoms (fever, pruritus, night sweats) and symptoms associated with splenomegaly (abdominal pain, early satiety, fatigue, secondary cytopenias due to splenic sequestration). However, it does not alleviate the bone marrow fibrotic process or prolong the survival of patients diagnosed with MF. (19) (20)

Fedratinib is indicated for disease-related splenomegaly or symptoms in primary myelofibrosis (PMF), post-polycythemia vera (PV)-related myelofibrosis, and post-essential thrombocythemia (ET)-related myelofibrosis in patients who are JAK inhibitor naïve or have been treated with Ruxolitinib. It is, nevertheless, less commonly used as first-line therapy than its JAK inhibitor counterpart, Ruxolitinib, due to concerns about toxicity and, most notably, Wernicke encephalopathy. (21)

Ropeginterferon alfa-2b has been approved as monotherapy for adult patients with PV who do not have symptomatic splenomegaly. Better control of haemoglobin and hematocrit levels leads to fewer patients undergoing repeated phlebotomy, thus avoiding the depletion of iron reserves. (22)

Currently, Hydroxyurea remains the most commonly used first-line agent in myeloproliferative neoplasms (MPNs), particularly polycythemia vera (PV) and essential thrombocythemia (ET), with a high risk of thromboembolic complications. (23) An alternative for treating ET is Anagrelide, which is often tolerated at lower doses. Unlike Hydroxyurea, it has a much lower risk of developing a second neoplasia. (24)

Low-risk PV patients should be treated with low-dose aspirin and phlebotomy to minimise the symptoms and complications associated with hyperviscosity. This is also the ideal therapeutic approach for patients with ET who have not been diagnosed with acquired von Willebrand disease. (23) Most importantly, adapting and maintaining a healthy lifestyle is mandatory to avoid further complications.

This study aims to present our centre's experience in the diagnosis and prognosis of BCR::ABL1-negative MPNs; treatment was initiated according to the current guidelines for PV, ET, PMF.

Material and methods

We conducted a retrospective, unicentric study at Coltea Clinical Hospital between January 2022 and September 2024, including 154 patients aged 18 and above who were newly diagnosed with PV, ET, PMF, and MPN-U.

Demographic data, including age, gender, environment and medical history, were collected.

Further data included a complete blood count, peripheral blood smear analysis, liver and renal function markers, iron reserve status, inflammatory markers, and genetic testing for JAK2V617F, CALR, and MPL mutations. An initial abdominal imaging study, such as a CT scan or Ultrasonography, was performed to evaluate splenomegaly.

The diagnosis was established based on histopathological results of bone marrow biopsy, with all data required to meet the 2022 WHO guidelines' major and minor diagnostic criteria.

When selecting the best therapeutic approach, the clinical presentation, grade of bone marrow fibrosis, mutational profile, splenomegaly, comorbidities, and disease-associated thromboembolic complications were taken into consideration.

Data collection and statistical analysis were made using Microsoft Excel. Results are presented as median and interquartile range for continuous variables with a non-parametric distribution, or absolute frequency and percentage of the total group for categorical variables.

RESULTS

In our study, 49 patients with PV, 49 with ET, 47 with MF, and 9 with MPN-Us were diagnosed according to the 2022 WHO-HAEM5/ 2022 ICC criteria. The age at diagnosis ranged from 20 to 90 years, with a median of 67 years. 31.82% were diagnosed with PV, and 31.82% were diagnosed with ET, respectively. 30.52% presented as MF, two-thirds of which (20.13%) were diagnosed in the prefibrotic stage. 5.84% of cases were unclassifiable. (Table 1).

Two patients (1%) diagnosed with PMF developed monoclonal gammopathy of undetermined significance (MGUS), and 1 (1%) presented with an associated small lymphocytic lymphoma (SLL). There was a single case of AML transformation.

According to data on the driver-gene mutational status, 43/49 (87.76%) of PV-diagnosed patients were JAK2V617F-positive, while 6/49 (12.24%) presented as triple-negative. Among the ET study group, 36/49 (73.47%) were JAK2V617F positive, 9/49 (18.37%) were CALR mutated, 2/49 (4.08%) were MPL mutated, and 2/49 (4.08%) were triple negative. 24/31 (77.42%) prefibrotic PMF-diagnosed patients were JAK2V617F-positive, 1/31 (3.23%) were CALR-positive, 2/31 (6.45%) were MPL-positive, while 4/31 (12.09%) were triple-negative. In the overt fibrotic stage, 10/16 (62.50%) were JAK2V617F-positive, 2/16 (12.50%) were MPL mutated, and 4/16 (25.00%) were triple negative. Among the unclassifiable cases, 6/9 (66.67%) were triple negative, and 3/9 (33.33%) presented the JAK2V617F mutation (Table 1).

At diagnosis, 44 patients were documented with splenomegaly, 15 of whom were diagnosed with pre-fibrotic myelofibrosis, followed by PMF- overt fibrotic cases (12). The PV group registered 9 instances; the lowest rate of splenomegaly was observed amongst the ET group (3). (Table 1)

	POLYCYTHEMIA VERA	ESSENTIAL THROMBOCYTEMIA	PMF, EARLY/PREFIBROTIC STAGE	PMF, OVERT FIBROTIC STAGE	MPN-U
Rate of diagnosis (%)					
	49 (31.82%)	49 (31.82%)	31 (20.13%)	16 (10.39%)	9 (5.84%)
Age at diagnosis					
<40 y	-	5/49 (10.20%)	1/31 (3.23%)	-	-
41-50 y	7/49 (14.29%)	7/49 (14.29%)	1/31 (3.23%)	1/16 (6.25%)	1/9 (11.11%)
51-60 y	12/49 (24.49%)	6/49 (12.24%)	12/31 (38.71%)	3/16 (18.75%)	1/9 (11.11%)
61-70 y	12/49 (24.49%)	12/49 (24.49%)	7/31 (22.58%)	4/16 (25.00%)	3/9 (33.33%)
71-80 y	13/49 (26.53%)	14/49 (28.57%)	9/31 (29.03%)	5/16 (31.25%)	3/9 (33.33%)
>80 y	5/49 (10.20%)	5/49 (10.20%)	1/31 (3.23%)	3/16 (18.75%)	1/9 (11.11%)
Diagnosis-related gender distribution					
Male	26/49 (53.06%)	13/49 (26.53%)	12/31 (38.71%)	11/16 (68.75%)	4/9 (44.44%)
Female	23/49 (46.94%)	36/49 (73.47%)	19/31 (61.29%)	5/16 (31.25%)	5/9 (55.56%)
Detected driver mutation					
JAK2V617F	43/49 (87.76%)	36/49 (73.47%)	24/31 (77.42%)	10/16 (62.50%)	3/9 (33.33%)
CALR	-	9/49 (18.37%)	1/31 (3.23%)	-	-
MPL	-	2/49 (4.08%)	2/31 (6.45%)	2/16 (12.50%)	-
Triple negativity	6/49 (12.24%)	2/49 (4.08%)	4/31 (12.90%)	4/16 (25.00%)	6/9 (66.67%)
Documented splenomegaly at diagnosis					
	9/49 (18.37%)	3/49 (6.12%)	15/31 (48.39%)	12/31 (38.71%)	5/9 (55.56%)

***Table 1**: MPN subtypes baseline characteristics*

The frequency of thrombosis appears to be higher in patients with PV (48.48%) and ET (33.33%), resulting in a total rate of 21% of the 154 MPN cases. Bleeding events, most notably gastrointestinal, occurred in 5% of the cases, most notably in patients diagnosed with PMF (2, 28.57% in early/pre-fibrotic stage, 2, 28.57% in overt fibrotic MF) (Table 2). Thrombotic risk factors are listed in Table 3.

	PV	ET	PMF, early/pre-fibrotic stage	PMF, overt fibrotic stage	MPN-U
Thrombotic events	16 (48.48%)	11 (33.33%)	5 (15.15%)	1 (3.03%)	-
Hemorrhagic events	2 (28.57%)	1 (14.29%)	2 (28.57%)	2 (28.57%)	-

Table 2: *Rate of vascular events in MPN-diagnosed patients*

	POLYCYTHEMIA VERA	ESSENTIAL THROMBOCYTEMIA	PRIMARY MYELOFIBROSIS	MPN-U
PATIENT-RELATED RISK FACTORS				
• **Age >60 years**	30	31	29	7
• **Previous thrombotic episode**	16	11	6	-
• **Cardiovascular Risk Factors**	30	23	27	7
• **Male sex**	26	13	23	4
DISEASE-RELATED RISK FACTORS				
• **Elevated white blood cell count (WBC>10 x 109/L)**	27	23	31	3
• **Presence of JAK2V617F mutation**	43	36	34	3
• **Elevated hematocrit**	44	5	11	1

Table 3*: Thrombosis risk factors*

According to the classical risk stratification, 13 of 49 (26.53%) patients diagnosed with PV were under 60 years and lacked a previous history of thrombosis, while 36 of 49 (73.47%) presented with high-risk disease (Table 4). At least one thrombotic event before diagnosis was registered for 16 patients (Table 2).

The International Prognostic Score for Essential Thrombocythemia (IPSET) classifies ET-diagnosed patients into three groups according to thrombosis risk: low, intermediate and high risk. More than half of the ET group was presented as high risk at diagnosis (27/49, 55.1%) (Table 4), of which eleven patients were stratified as intermediate-high risk due to a history of thrombosis (Table 2).

PMF patients were evaluated at diagnosis according to the International Prognosis Scoring System (IPSS). Stratification for the four risk groups is presented in Table 4. The Dynamic International Prognosis Scoring System (DIPSS) was also applied at diagnosis, as modification of the score during further evaluation can be a predictor for leukemic transformation. 57.45% presented as Intermediate-1 risk. DIPSS Plus was, however, not used as a risk calculator due to a lack of data regarding karyotype.

Classical risk stratification for PV (ELN recommendations): **Age over 60 years** **Thrombosis history**	
Low-risk disease:	13/49 (26.53%)
High-risk disease:	36/49 (73.47%)
IPSET- Thrombosis risk for ET: **Age over 60 years (1)** **Thrombosis history (2)**	

Cardiovascular risk factors* (1) JAK2V617F mutation detected (2)	
Low-risk (0-1 pts)	7/49 (14.29%)
Intermediate risk (2 pts)	15/49 (30.61%)
High Risk (3-6 pts)	27/49 (55.10%)

IPSS/DIPSS Scoring Systems for Myelofibrosis Age > 65 years WBC count>25 x 10^9 /L Haemoglobin < 10g/L Peripheral blood blasts ≥ 1% Constitutional symptoms			
IPSS		**DIPPS**	
Low-risk (0 pts)	9/47 (19.15%)	**Low risk (0 pts)**	9/47 (19.15%)
Intermediate-1/ INT-1 risk (1 pts)	15/47 (31.91%)	**Intermediate-1/ INT-1 risk (1-2 pts)**	27/47 (57.45%)
Intermediate-2/ INT-2 risk (2 pts)	13/47 (27.66%)	**Intermediate-2/ INT-2 risk (3-4 pts)**	9/47 (19.15%)
High-risk (≥3 pts)	10/47 (21.28%)	**High risk 5-6 pts)**	2/47 (4.26%)

***Cardiovascular risk factors include hypertension, diabetes mellitus and dyslipidemia**
ELN, European LeukemiaNet
IPSET, International Prognostic Score for Essential Thrombocythemia
IPSS, International Prognosis Scoring System
DIPSS, Dynamic International Prognostic Scoring System
WBC, White Blood Cell

Table 4: *Prognostic Scores and Risk Stratification for PV, ET, PMF*

Out of the 128 patients who required specific treatment beyond low-dose aspirin/ anticoagulants, 107 were initiated on Hydroxyurea (40 PV, 34 ET, 30 PMF, 3 MPN-U), and 6 ET-diagnosed patients were treated with Anagrelide. Two patients diagnosed with PV received first-line Ropeginterferon alfa-2b. Ruxolitinib was administered in 10 cases of PMF, while Fedratinib was initiated in 3 PMF cases (Table 5).

Amongst the studied group, 45 PV cases, 5 ET patients, 9 pre-PMF, 1 PMF (MF grade 2-3) and 1 MPN-U required multiple phlebotomies. 12 patients presented with severe anaemia that necessitated blood transfusions (7 PMF, 5 MPN-U). 10 patients presented adverse reactions: 2 presented with cutaneous toxicity after Hydroxyurea use, 1 case of anaemia post-administration of Hydroxyurea, 3 cases of gastrointestinal side-effects of Hydroxyurea, 1 case of ischemic stroke after Anagrelide use, 3 cases of anaemia post-administration of Ruxolitinib. 22 patients required second-line therapy as illustrated in Table 5.

	POLYCYTHEMIA VERA	ESSENTIAL THROMBOCYTEMIA	PRIMARY MYELOFIBROSIS	MPN-U
INITIAL MANAGEMENT AND PRIMARY PREVENTION				
CYTOREDUCTIVE THERAPY				
Hydroxyurea	40	34	30	3
Anagrelide	-	6	-	-
Ropeginterferon alfa-2b	2	-	-	-
JAK INHIBITORS				
Ruxolitinib	-	-	10	-
Fedratinib	-	-	3	-
Antiplatelet-therapy/ Anticoagulation only	7	9	4	6
THERAPEUTICAL SWITCH				

CYTOREDUCTIVE THERAPY				
Hydroxyurea	-	2[1]	-	-
Anagrelide	-	4[2]	-	-
Ropeginterferon alfa-2b	8[3]	-	-	-
JAK INHIBITORS				
Ruxolitinib	1[4]	-	5[5]	-
Fedratinib	-	-	2[6]	-

[1] Ischemic stroke post-Anagrelide use
[2] Hydroxyurea-associated cutaneous or GI toxicity
[3] Monthly phlebotomy needed
[4] Anaemia post Hydroxyurea
[5] Persistence of night sweats, fatigue. 3 persistent splenomegaly
[6] Persistent splenomegaly

***Table 5**: Management and prevention*

Discussions

The primary focus of this study is the diagnosis of BCR::ABL1-negative MPNs, such as polycythemia vera, essential thrombocythemia and primary myelofibrosis, while also considering MPN, unclassifiable entities, according to the latest international guidelines.

Despite the lack of symptoms at diagnosis, with most patients being redirected for a haematological check-up after abnormal routine blood tests, more than half were included in a higher-risk group. Over 70% of the patients diagnosed with PV were high-risk at diagnosis and required multiple phlebotomies and cytoreductive therapy, and only 14% of the ET group presented as low risk. PMF presented primarily as intermediate 1/2 according to the IPSS/DIPSS risk stratification.

Furthermore, the triple negative genotype is currently more prevalent within the BCR::ABL1-negative myeloproliferative neoplasms, raising the importance of histopathological examination of the bone marrow sample at diagnosis. While triple-negative ET is usually more indolent, triple-negative PMF presents a more aggressive course with a higher rate of leukemic transformation. (25)

For PV-diagnosed patients, cytoreduction with Hydroxyurea remains the preferred first-line treatment. ELN, however, recommends pegylated interferon-alfa as cytoreductive treatment in younger PV patients. (26) Phlebotomy therapy alleviates short-term hyperviscosity-associated symptoms, but not pruritus or erythromelalgia. (27)

Most patients with ET can be monitored for months or even years before treatment is needed, especially under the age of 60 with no history of thrombosis. High-risk patients are typically started on cytoreductive therapy with Hydroxyurea or Anagrelide, in combination with Aspirin. (28) In our study 42 patients were classified as intermediate/high risk, 40 of which required cytoreduction. Treatment election was based on age, comorbidities, level of thrombocytosis and individual tolerance.

MF-diagnosed patients frequently require supportive therapy for anaemia, splenomegaly and its associated symptoms. (26) The hydroxyurea dosage is lower than in PV or ET. JAK2 inhibitors have shown a response in reducing spleen size and alleviating associated symptoms, though they do not have curative potential. (2) Fifteen patients out of the studied lot received Ruxolitinib either as first or second-line treatment, with only two patients experiencing persistent constitutional symptoms due to splenomegaly that required electing to initiate fedratinib.

MPN-U remains challenging due to the lack of agreed-upon monitoring and therapeutic guidelines. However, new advances in molecular and histopathological fields have, to some extent, reduced the number of underdiagnosed patients. Future developments may provide more conclusive diagnostic criteria. (5)

Conclusion

Philadelphia-negative myeloproliferative neoplasms have benefited from emerging therapies in recent years, which have not only prolonged life expectancy but also improved the quality of life.

However, MPNs can cause significant morbidity in the form of burdensome symptoms, potentially fatal cardiovascular complications or progression to more

aggressive disease (over time, presenting the risk of progressing to secondary myelofibrosis and finally, to acute myeloid leukaemia).

The primary goal in treating MPNs remains to prolong patients' survival, improve the quality of life, while reducing the incidence of thrombotic and hemorrhagic events and minimising constitutional symptoms.

Diagnosis of myeloproliferative neoplasms remains challenging. The current extended criteria for diagnosis may aid in identifying previously undiagnosed patients, and future development in molecular profiling may enable the prediction of prognosis and guide further therapeutic decisions, especially among MPNs with undistinguishable biological features.

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

The study has received approval of "Coltea" Clinical Hospital Ethical Committee no. 43/2025.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/ or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

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