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MINIREVIEWS

Acute myocardial infarction in myeloproliferative neoplasms

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Abstract

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of hematologic malignancies characterized by an abnormal proliferation of cells of the myeloid lineage. Affected individuals are at increased risk for cardiovascular and thrombotic events. Myocardial infarction (MI) may be one of the earliest clinical manifestations of MPNs or may be a thrombotic complication that develops

during the natural course of the disease. In the present review, we examine the epidemiology, pathogenesis, clinical presentation, and management of MI in MPNs based on the available literature. Moreover, we review potential biomarkers that could mediate the MI-MPNs crosstalk, from classical biochemical tests, *e.g.*, lactate dehydrogenase, creatine kinase and troponins, to pro-inflammatory cytokines, oxidative stress markers, and clonal hematopoiesis.

Key Words: Myeloproliferative neoplasms; Polycythemia vera; Essential thrombocythemia; Myelofibrosis; Myocardial infarction; Acute coronary syndrome; Biomarker; Clonal hematopoiesis

Core Tip: Patients diagnosed with myeloproliferative neoplasms (MPNs) are at risk of developing thrombotic complications, among which acute coronary syndromes are of relevance. Myocardial infarction (MI) can emerge as the initial event in the diagnosis of MPNs or occurs during the evolution of the disease. Here, we examine the interplay between MI and MPN, with a focus on the epidemiology, presentation, risk factors, diagnosis, and management of MI in MPNs, as well as discuss potential biomarkers of MI in MPNs, as well as the role of inflammation and clonal hematopoiesis.

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) are a heterogeneous class of blood disorders characterized by an abnormal proliferation of cells of the myeloid lineage[1]. They comprise a group of chronic myeloid malignancies with various phenotypes, marked by the clonal proliferation of hematopoietic stem cells and excessive proliferation of terminally differentiated myeloid blood cells[2]. The four classic types of MPNs include chronic myeloid leukemia, essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)[1]. Furthermore, chronic neutrophilic leukemia, chronic eosinophilic leukemia, and unclassified MPN are also included in the classification presented by the World Health Organization (WHO)[1]. Among these, PV (characterized by an absolute increase in erythrocytes due to the proliferation of the erythroid lineage[3]), ET (marked by the excessive proliferation of hyperlobulated mature megakaryocytes in the bone marrow along with persistent peripheral blood thrombocytosis[4]) and PMF (characterized by abnormal differentiation of the megakaryocytic clone, ultimately resulting in excessive proliferation of reactive fibroblasts and fibrosis[5]) are BCR-ABL1 negative and will remain the focus of this review. The major cause of morbidity and mortality in MPNs are thrombo-hemorrhagic complications. This review aims to describe the complex pathogenesis, risk stratification, diagnostic criteria, and management of acute coronary syndrome (ACS) in MPNs.

Patients with MPNs have a higher risk of cardiovascular events[6]. It is important to note that ACS can be one of the first clinical manifestations of MPN[7], or it can be a thrombotic complication of ET and PV. PV typically affects the large arteries of the cardiovascular and cerebrovascular system, while ET tends to involve the microcirculatory system[7]. Previously published literature suggests that the reported incidence of cardiovascular complications related to MPNs ranges from 4% to 21%[7]. In patients diagnosed with ET, the incidence of thrombosis was reported to be 25%, with arterial thrombosis occurring more frequently than venous thrombosis[8]. During the follow-up of patients with PV, over a 10-year period, coronary events were frequently observed, with a reported rate of 11.4%[3]. Among a total of 1213 PV patients, thrombosis was identified in 19% of cases over a 20-year period, with 21.7% thrombotic events resulting in myocardial infarction (MI)[9]. In patients diagnosed with ET and PV, the mortality rate attributed to cardiovascular disease was 26% and 25%, respectively, higher than the mortality rate caused directly by the disorder itself[10]. Cerebral venous thrombosis, although a rare complication of PV, has been reported to cause the death of 8.3% of patients[11]. Furthermore, complications of MI may develop in 12 mo after the diagnosis of ET or PV[12].

Pathogenesis

The mechanisms responsible for the increased tendency for thrombosis in MPNs are not yet fully understood. ACS in myeloproliferative diseases is mostly attributed to coronary thrombosis due to hyperviscosity and thrombocytosis. The etiology of MPN-related hemostatic conditions is complex and multifactorial, involving a combination of quantitative and qualitative changes[12]. Pathophysiological mechanisms likely involve complex interactions between blood components and vascular cells, together with hemodynamic changes[13]. These, coupled with risk factors such as advanced age, a history of thrombotic events, leukocytosis, and cardiovascular risk factors such as hypertension, smoking, diabetes mellitus, have been observed to increase the risk associated with developing thrombosis in the context of myeloproliferative diseases. Factors that contribute to the thrombophilic state in MPNs include: Increased cell mass resulting from

the clonal expansion of hematopoietic stem cells[11]; prothrombotic state induced by increased platelet accumulation, along with the release of activation products and increased expression of surface activation markers[5]; elevated leukocyte count, which has been documented to be a stronger predictor of thrombogenesis than platelet count or hematocrit/hemoglobin levels[13]; elevated blood viscosity that pushes platelets centrifugally, causing them to adhere to the vessel wall, consequently initiating the process of thrombus formation; increased tendency of erythrocytes to attach to the endothelium; inflammatory response resulting from increased cytokine expression; and an elevated level of microparticles exhibiting procoagulant activity[14].

Furthermore, in most patients with MPN, driver mutations are observed in the pro-inflammatory JAK-STAT signaling pathway, with *JAK2* mutations the most prevalent. MPN patients carrying *JAK2* mutations are at higher risk of developing arterial thrombosis[6], which is evident in reports that around > 95% PV and approximately 50% of patients with ET and PMF have a mutation of the *JAK2* gene, *i.e.*, *JAK2V617F*[2,11]. In addition to mutations in exon 14 of the *JAK2* gene, deletions, and mutations in exon 12 of the *JAK2* gene have been observed. Furthermore, mutations in *MPL*, the thrombopoietin receptor gene, as well as in *CALR*, the calreticulin gene, have been identified along with several mutations in non-driver genes, for example, the ten-eleven translocation 2 gene[2,14]. Although a susceptibility haplotype to *JAK2* mutations, 46/1, haplotype, has been reported, the presence of a *JAK2* mutation is not strictly associated with the initialization of MPN[2].

RISK FACTORS FOR ACS/MI IN MPNS

Patients with MPNs have an overall increased risk of developing cardiovascular disease, especially under the spectrum of ACS[15,16]. The incidence of ACS in these patients has been attributed to significant morbidity and mortality, with up to 76% of deaths due to cardiovascular events and approximately 32% having major adverse cardiovascular events up to 1 year post-ACS[6]. As discussed above, the basis for ACS and MPNs comorbidity is largely due to the prothrombotic, pro-inflammatory, and profibrotic states seen in patients with MPNs secondary to gain of function mutations in the *JAK* signaling pathway[14,16].

Risk factors for ACS in MPNs are chiefly based on the level of ischemic risk, classified as either; high, intermediate or low, based on a set of established criteria[17-19]. Increasing age, previous thrombosis, and diabetes have been identified as consistent and independent predictors of cardiovascular events in MPNs and therefore have been classified as the main risk factors for ischemic events in MPNs[17]. Minor risk factors in this criterion include smoking, hypertension, and hypercholesterolemia. Therefore, a high-risk patient is often < 60 years of age, has a history of thrombosis, or diabetes. Intermediate-level risk patients have ages between 40 and 60 years along with one of the minor risk factors or an age < 40 years with two minor risk factors. Patients with a low-risk level do not have any identifiable risk factors[4]. A schematic representation of the risk factors that contribute to the development of ACS in MPNs is depicted in Figure 1.

The European Collaboration on Low-Dose Aspirin in Polycythemia (ECLAP) study reported higher incidences of cardiovascular complications in patients with PV > 65 years (5% patient-years) and in those with a history of thrombosis (4.93% patient-years) compared to younger patients without a history of thrombosis (2.5% patient-years)[20]. Similarly, Barbui *et al*[21] based on the results of an epidemiological study of 1638 patients with PV, observed an 8:6 hazard ratio in patients > 60 years compared to younger patients. Carobbio *et al*[22] observed a similar trend in an international study of 891 patients with emergency department (ED) where individuals over 60 years of age and with a thrombotic history had risk ratios (RR) of 1.5 and 1.93, respectively, to develop major thrombosis when followed for about 6.2 years.

Another risk factor for the thrombosis and MI in MPN patients is leukocytosis[17]. A study using data from the ECLAP database assessed the association between hematological variables and risk of MI[23]. They observed a 70% increased risk of thrombosis in patients with PV with a white blood cell (WBC) count > 15 × 10^9/L. The proposed mechanism of thrombosis is believed to involve endothelial inflammation from activated WBCs. Consequently, the consensus recommends that as part of the cytoreduction in PV and ET, the WBC count should remain within the normal range[24]. It is noteworthy, however, that this association has not yet been proven in randomized clinical trials. Interestingly, while elevated platelet levels can be assumed to be the leading risk factor for MI in these patients, the findings of the ECLAP study showed that neither the proposed therapeutic target (400 × 10^9/L) nor other platelet count thresholds served as a predictor of increased risk of the aforementioned complication[25].

Most minor risk factors for the occurrence of MI in MPNs constitute conventional atherosclerosis risk factors and serve as accentuators in the background of the aforementioned major risk factors leading to the transition from low to intermediate or high-risk levels[26,27]. The International Prognostic Score for Thrombosis categorizes cardiovascular risk factors as part of the variables that are significantly and independently associated with increased rates of thrombosis in patients with ED[26]. Genetic interplay in the causality of MI in MPNs is also to be considered as key risk factors. A study evaluating PV patients observed a higher risk of cardiovascular events (RR = 7.1; P = 0.003) in patients harboring > 75% of the mutant allele JAK2V617F[28]. Similarly, a systematic review showed a twice as high odds (odds ratio = 1.92; 95% confidence interval: 1.45-2.53) in patients with similar mutations in ET, although heterogeneity between included studies [29]. The coexistence of this mutation with leukocytosis results in the highest levels of fatal and non-fatal thrombosis[30].

CLINICAL PRESENTATION

Approximately 0.27% and 0.1% of MI-related hospitalizations due to thrombosis are attributed to ET and PV, respectively [31]. Thus, despite the relatively high incidence of this vascular complication in MPNs, it contributes very little to the

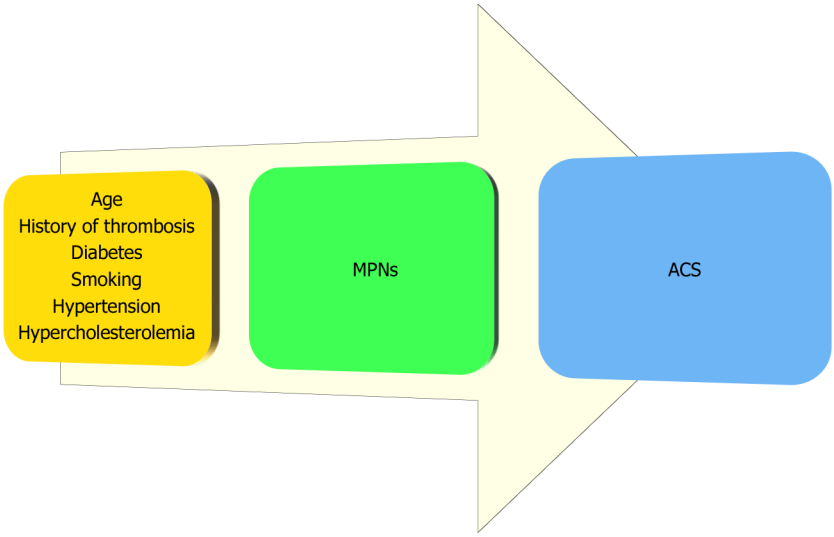

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Figure 1 Schematic representation of the risk factors that contribute to the development of acute coronary syndromes in myeloproliferative neoplasms. MPNs: Myeloproliferative neoplasms; ACS: Acute coronary syndromes.

etiology of MIs. ACS has been reported as the initial presentation in some patients with MPN; however, most incidences of MI develop within one year after diagnosis of ET and PV[12]. This usually occurs despite the initiation of MPN treatment. Patients usually present with the typical symptoms associated with MI, that is, severe retrosternal chest pain radiating to the shoulder that is squeezing in character, exertional chest pain, dyspnea combined with profuse sweating. These patients often lack a history of risk factors associated with ACS, *e.g.*, hypertension, diabetes, or hyperlipidemia; however, one or more may be present[32]. They may or may not have a family history of coronary artery disease or a history of smoking with varied pack-years. Other associated symptoms include headache prior to acute condition, nausea, general malaise, and diaphoresis[32].

Examination and lab findings often vary from patient to patient. Vital signs including heart rate, blood pressure, temperature, respiratory rate, and oxygen saturation often remain stable within the reference ranges. Lung auscultation is often clear throughout both lungs, however, cardiac examination at times reveals an S4 gallop[33] and splenomegaly may at times be palpable on abdominal examination[34]. The peripheries do not show edema, but erythromelalgia of the hands is positive in some cases[33]. Lab tests reveal elevated platelets, troponins, D-dimers, triglycerides and hematocrit with low potassium levels and normal urea, electrolytes, and creatinine[35,36].

On radiological investigation, the thrombus in ET is often located within the left anterior descending artery; however, right coronary involvement has also been reported in the literature[36,37]. Electrocardiography usually shows a regular sinus rhythm with elevation of the ST or non-ST segment[33,34]. Notably, as part of treatment, an oral imidazoquinazoline drug, anagrelide, has been observed to cause ACS in some (1%-5%) patients with ED by directly inducing coronary artery vasospasm[4]. The incidence of ACS increases with increasing age; therefore, most of the presenting patients are over 60 years of age and those with a history of thrombosis or in the background of mutations in the *JAK2* or *MPL* genes[35].

DIAGNOSIS

For ACS, risk factors such as age, family history of coronary artery disease, hypertension, diabetes, dyslipidemia, or smoking should be considered[7]. An electrocardiogram should be performed to assess the type of MI to guide emergency management. Cardiac markers may be elevated[38]. Coronary angiogram may reveal the coronary artery involved, of which the most reported in MPNs is the left anterior descending artery[7]. Echocardiography may be performed to assess ventricular ejection fraction[7].

The complete blood cell count becomes an important baseline investigation, particularly in this case. Lab tests may reveal an increase in platelet count, an increase in hematocrit, and/or leukocytosis. However, reactive thrombocytosis and leukocytosis can be observed due to an inflammatory response in the case of acute MI, resulting in a delayed or missed diagnosis of MPN[7]. The international normalized ratio and prothrombin time may be normal[39]. In addition, giant platelets and megakaryocyte fragments can be seen in the peripheral blood smear[39].

Diagnosis of ET according to the criteria issued by the WHO is given by a persistent elevation of the platelet count of ≥ 450×10^9 platelets/L, presence of typical mutations associated with ET, a negative translocation of BCR-ABL1 and bone marrow biopsy for histopathological confirmation. Molecular biology studies for *JAK2* mutations confirm the diagnosis, as evidence of the *JAK2V617F* mutation has been observed in 60% of patients with ET[7]. In the analysis of the *CALR* or *MPL* mutations, mutations of the *CALR* exon 9 and *MPL* exon 10 have been reported in 30% of patients who are *JAK2V617F* negative[7]. Cellular bone marrow with maturing trilineage hematopoiesis and large atypical hypolobulated

megakaryocytes may be seen in bone marrow biopsy, as reported in previously published literature[39].

Furthermore, the abdomen should be examined for hepatosplenomegaly, which may be indicative of thrombocytosis, leukocytosis, or polycythemia, followed by abdominal ultrasound if indicated[7]. The following three 'red flags' have been reported in previous literature that should raise suspicion of ET in ACS and should therefore inform relevant investigations, including bone marrow biopsy and genetic testing for driver mutations[40]: (1) There are few or no coronary artery disease-related risk factors present in ACS patients; (2) Platelet count > 450 × 10^9/L. A mild increase above this level should also warrant investigation; and (3) In coronary angiography, severe atherosclerotic narrowing is not reported. However, thrombotic occlusion may sometimes be observed.

PV is diagnosed when the three main criteria are met, or when the patients meet the first two main criteria and the minor criterion defined by the WHO[3]. The main criteria for PV issued by the WHO include: (1) Hemoglobin level > 16.5 g/dL in males, and > 16.0 g/dL in women or a hematocrit > 49% in males and > 48% in women or increased red cell mass; (2) Hypercellularity for age with trilinear growth observed on bone marrow biopsy; (3) Detection of *JAK2* mutations (V617F or exon 12 mutations). The minor criterion includes a decreased serum erythropoietin level[3]. In patients with PMF, circulating platelets exhibit an activated state and demonstrate notably elevated levels of protein kinase Cepsilon (PKCepsilon)[41]. Furthermore, in patients with MF, PKCepsilon levels in platelets were found to be associated with high-risk disease and a history of major cardiovascular events[41].

MANAGEMENT

For patients with ACS, emergency management should begin depending on the specific type of MI. ACS management in ET involves initiating cytoreductive therapy, administration of antithrombotic drugs, and revascularization based on risk-oriented recommendations. Thus, risk stratification of thrombosis becomes important to guide management. Patients are classified as 'high risk' when any of the three specified criteria is met: (1) Age ≥ 60 years; (2) A previous history of thrombosis or major bleeding; and (3) A blood platelet count of ≥ 1500 × 10^9/L[40]. Patients are labeled low risk if their age is less than 60 years and there is no history of previous thrombotic event[12].

As all patients with ACS with ET are classified as 'high risk'[40], their management involves monitoring the associated risk factors and initiating cytoreductive therapy. The first-line drug is hydroxyurea and the objective of the therapy is to maintain a platelet target of less than 400 × 10^9/L[42]. Platelet target count of 400 × 10^9/L is generally considered acceptable by most hematologists; however, a target count of 600 × 10^9/L may be appropriate to avoid anemia and leukocytopenia, and in particularly younger patients, malignant transformation possibly related to intensive cytoreductive therapy can be prevented[40]. With long-term administration of hydroxyurea, irreversible gonadal toxicity has been reported[42]. Therefore, in younger patients with reproductive intentions, interferon alpha is preferred[42]. In addition, limited information is available on the safety of cytoreductive therapy in very elderly patients[12].

Given the risk of thrombosis with the *JAK2V617F* mutation and cardiovascular risk factors, cytoreductive therapy may be combined with antiplatelet therapy with low-dose acetylsalicylic acid. The combination of cytoreductive therapy with antiplatelet agents or oral anticoagulants has also been reported to be more effective than the administration of single drugs[43]. Furthermore, the JAK1/2 inhibitor ruxolitinib has also been used in the management of ET[44]. Platelet reducing agents such as anagrelide can also be prescribed[43]. Anagrelide (imidazoquinazoline) selectively affects megakaryocytes by inhibiting cyclic-AMP phosphodiesterase III activity, resulting in inhibition of platelet aggregation. Although it is recommended for patients resistant to or intolerant to hydroxyurea, it can induce spasm of the coronary arteries, leading to cardiovascular events such as ACS, heart failure, and/or arrhythmias[4].

The estimate of the rate of recurrence of thrombosis after cytoreductive therapy was halved in the overall cohort of 494 patients with PV and ET[43]. In addition, the use of tirofiban, a glycoprotein IIb/IIIa receptor blocker, has also been highlighted in the treatment of acute MI in an ET patient[45]. Thrombotic complications in PV are substantially reduced by cytoreductive management of blood hyperviscosity either by phlebotomy or chemotherapy along with antiplatelet therapy using low-dose aspirin to achieve target hematocrit levels below 45%[44].

Other treatment options for ED include aspiration thrombectomy and distal protection revascularization to prevent distal embolization. Percutaneous coronary intervention has been described as an effective approach to revascularization in patients with ER, however, an increased incidence of complications such as stent thrombosis and restenosis has been reported[8]. However, cytoreduction is advised before revascularization to prevent platelet activation and future thrombotic events[39]. The management of ACS in MPNs is therefore a combination of aggressive pharmacotherapy and an appropriate revascularization approach.

PROGNOSIS

Thrombosis remains the most common complication of MPNs. There is an increased risk of in-hospital mortality due to MI associated with ET and PV. It has been reported that around 4% of patients with MPNs die from MI[46]. The incidence of recurrence of thrombosis after previous arterial or venous thrombosis is high, with studies reporting a rate of 33%[47]. Furthermore, in patients with ACS due to this pathological hypercoagulable state, a diagnosis may be missed in the absence of marked thrombocythemia as clinicians focus on the restoration of normal cardiac function and coronary vessel revascularization and thus may overlook this rare etiology[46]. Thus, recurrence can further worsen the prognosis for this condition. The prognosis also worsens with increasing age, the presence of atherosclerotic risk factors, the presence of a previous thrombotic event, and comorbid conditions[32]. Treatment must therefore involve a multidisciplinary team in

order to treat the underlying etiology, prevent recurrence, and decrease the risk of additional thrombotic complications.

FUTURE PERSPECTIVES: CAN WE QUEST FOR BIOMARKERS?

In the era of genomic and precision medicine, it is warranted to identify biomarkers that could predict the onset of thrombotic complications or link ACS and MPN. Lactate dehydrogenase is of poor utility in the ACS-MPNs interaction, as it is not an ideal biomarker for the heart and is also frequently detected in elevated concentrations in MPN[48]. Furthermore, creatine kinase, a potential marker of myocardial damage useful for its low execution costs as opposed to other more heart-specific biochemical panels, has been shown to exhibit a low mean creatinine kinase activity compared to ACS, healthy individuals and subjects diagnosed with a wide range of chronic disorders. However, Pan *et al*[49] have highlighted that creatinine kinase activity was the best biomarker for MPNs among 36 disorders, including ACS, stroke, diabetes, leukemia, lymphoma, multiple myeloma, and several solid cancers. Increased troponin concentrations have rarely been reported in MPNs. Tortorella *et al*[50] investigated cardiovascular risk factors and events in ET subjects prescribed anagrelide, discovering that only 2 of 55 analyzed patients had elevated troponin values. However, therapy with this platelet-lowering agent did not influence troponin concentrations nor the risk of MI, and the two individuals diagnosed with ET who also developed MI did not require discontinuation of anagrelide.

Oxidative stress could be a mediator of MPN-ACS crosstalk. Ischemia-modified albumin has been detected at elevated concentrations in both MI[48] and MPN[51-53]. Regardless of the disease subtype, MPN subjects showed increased albumin values modified by ischemia compared to healthy controls, with notable elevations exhibited by individuals with PMF and *ASXL1*-mutated MPN[51]. Similarly, Karahan *et al*[52] have highlighted that subjects living with PV show elevated levels of ischemia-modified albumin compared to healthy counterparts and that ischemia-modified albumin is an excellent predictor of tissue ischemia in PV. Additionally, prescription of ruxolitinib has been reported to decrease levels of oxidative stress in PMF. After one month of therapy, ischemia-modified albumin values decreased in PMF patients regardless of their mutational landscape. Subjects with PMF mutated with *ASXL1, JAK2V617F,* and *CALR*-mutated PMF (P = 0.001 for all), followed by *MPL*-mutated (P = 0.005) and triple negative PMF (P = 0.028)[53].

S100A, a myeloid-related protein, has also been reported in elevated values in ACS[48] and MPN. S100A is inhibited by pro-inflammatory cytokines and may emerge as a potentially relevant biomarker of inflammation in the diagnosis of MPN[54]. Furthermore, S100A proteins interact with cell signaling pathways in MPNs *via* Toll-like receptor 4 and RAGE in a burden-dependent manner of the *JAK2V617F* and *CALR* alleles, respectively[55]. Choline-related metabolites have been detected at high levels in ACS[48], however, Gómez-Cebrián *et al*[56] noted that there are low concentrations of these biomarkers in MPN.

Inflammation markers remain elevated in both ACS[48] and MPNs[57,58]. MPN inflammation is dependent and independent of the mutational landscape of the disease and is influenced not only by genetics, but also by the immune system, diet, metabolism, and comorbidities[59]. Furthermore, researchers have pointed out that both MPN patients[58] and MI subjects have elevated concentrations of ferritin[60,61], C-reactive protein[62,63], and fibrinogen[64]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin (IL)-6 and IL-1, and the NACHT, LRR, and PYD domains-containing protein 3 inflammasome have been reported to contribute to the pathogenesis of both MI[65-67] and MPN[58,59,68-70].

Dyslipidemia is recognized as a contributor to the development of MI[48]. In addition, several assessments have also delineated the role of lipid alterations in MPN. Furuya *et al*[71] have revealed that elevated levels of triglycerides and low-density lipoprotein-cholesterol are associated with thrombotic complications and survival in ET. Apolipoprotein A1 levels were also associated with the burden of the *JAK2V617F* allele in people with PV[72].

Clonal hematopoiesis of indeterminate potential has also emerged as a contributing factor to the onset of MI[73-75]. Moreover, inflammation has depicted as a possible link between the hematologic malignancies, thrombosis, and ACS in particular[76]. A schematic representation of potential biomarkers linking ACS and MPNs is depicted in Figure 2.

As new instruments are continuously being developed to evaluate cardiovascular risk, we may experience the beginning of an improved prognostication of thrombotic events in MPNs. For example, Mehta *et al*[77] have assessed the QRISK3 score in a cohort of 438 individuals diagnosed with MPNs, revealing that subjects with a history of arterial thrombosis have an elevated burden of cardiovascular risk factors and thus an increased cardiovascular risk warranting for a more aggressive management of associated comorbidities. The QRISK3 tool takes into consideration age (25-84 years), sex, ethnicity, smoking status, presence of comorbidities (diabetes, atrial fibrillation, chronic kidney disease stage 3-5, migraines, lupus, rheumatoid arthritis, severe mental illness, erectile dysfunction), family history of angina or AMI in a 1st degree relative aged < 60 years, use of several medications (antihypertensive agents, antipsychotics, oral corticosteroids, treatment for erectile dysfunction) and several other variables (body mass index, total cholesterol/high-density lipoprotein cholesterol ratio, systemic blood pressure values and the standard deviation of at least two most recent systolic blood pressure readings)[77]. Moreover, Skov *et al*[78] have highlighted that in MPNs there is a dysregulation of the genes involved in the onset of premature/accelerated atherosclerosis, depicting an aberrant expression of 45-56 out of 84 investigated genes. Thus, their findings might explain the crosstalk between inflammation and thrombosis in MPNs and the contribution of this axis to the onset of atherosclerosis and ACS in these blood cancers.

Nevertheless, Leiva *et al*[79] reported that 76% MPN patients are likely to experience another major cardiovascular event or even death following an episode of ACS. The researchers examined 41 individuals with MPNs and a history of ACS who were followed-up for 80 mo, demonstrating that the presence of leukocytosis [leukocyte count ≥ 20000 leukocytes/μL; hazard ratio (HR) = 9.10], the occurrence of ACS in the first year after the established diagnosis of MPN (HR = 3.84), the presence of JAK2 gene mutations (HR = 3.71) and history of cardiovascular disease (HR = 2.60) were risk

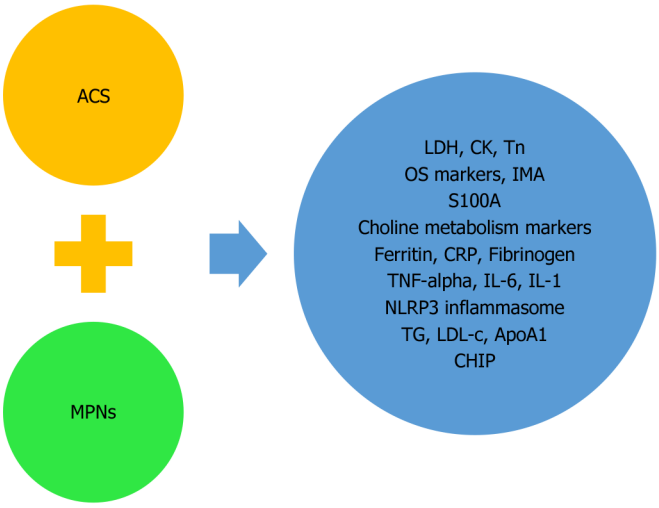

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Figure 2 Potential biomarkers linking acute coronary syndromes and myeloproliferative neoplasms. MPNs: Myeloproliferative neoplasms; ACS: Acute coronary syndromes; LDH: Lactate dehydrogenase; CK: Creatine kinase; Tn: Troponin; OS: Oxidative stress; 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.

factors for another major cardiovascular event or death in this MPN subpopulation[79]. These results are particularly interesting as the same group of scientists have previously reported that according to their propensity score analysis MPN patients who suffer an episode of AMI are less likely to experience in-hospital death and cardiac arrest but elevated rates of hemorrhages *vs* individuals who experienced an AMI but do not associate MPNs[80]. Therefore, based on these findings, we suggest a close monitorization and follow-up of individuals diagnosed with MPNs and who experience an episode of AMI.

CONCLUSION

MI remains a potentially fatal complication of MPNs and may be the presenting event in MPN diagnosis or develop during the natural course of the disease. Patients who develop MI and have persistent hematological abnormalities warrant screening for MPN. Driver mutations, inflammation, and clonal hematopoiesis may to contribute to the pathogenesis of MI in MPN. Future investigations should focus on the discovery of biomarkers that could predict the development of MI in MPN subjects, as well as indicate which MI patients could also suffer from blood cancers.

FOOTNOTES

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