

Problems of Insufficient Consideration of Genetic Thrombophilias (with focus on JAK2 mutation) in Thrombosis in Patients with Pancreatic Cancer

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Abstract

Background: Pancreatic cancer (PC) carries the highest risk of venous thromboembolic events (VTE) among all malignancies. Splanchnic vein thromboses (SVT) present a particular clinical challenge, often exhibiting resistance to standard anticoagulant therapy. Recent evidence suggests that a key reason for this resistance is the comorbidity of PC with myeloproliferative neoplasms (MPN), particularly the somatic JAK2 V617F mutation. However, contemporary clinical guidelines do not fully account for this factor, leading to systematic under diagnosis of a significant proportion of cases, inadequate prophylaxis and treatment of thromboses, and, consequently, worsened oncological outcomes.

Objective: A comprehensive analysis of the problem of under diagnosis of the JAK2 V617F mutation in PC patients with thrombosis, and the development of evidence-based proposals for optimizing diagnosis and therapy.

Materials and Methods: A systematic analysis of current international (NCCN, ESMO) and Russian clinical guidelines, retrospective cohort studies, and literature reviews on thrombogenesis in MPN and oncological diseases was conducted. Special attention was paid to studies investigating the frequency and clinical features of thrombosis in the comorbidity of solid tumors and MPN.

Results: The JAK2 V617F mutation was identified in a significant proportion of patients with splanchnic vein thromboses of unknown etiology (up to 20-40%). In patients with both PC and the JAK2 V617F mutation, the risk of VTE increases 3-4 times compared to PC alone. Thromboses in this group are characterized by an aggressive course: resistance to direct oral anticoag

ulants (DOACs), a high recurrence rate (up to 60-70% within one year), and a risk of transformation from occult MPN to overt forms. Significant gaps in guidelines were identified: neither NCCN, ESMO, nor Russian recommendations propose an active screening strategy for JAK2 V617F in PC patients. Diagnosis is hampered by the latent course of MPN, limited availability of testing, and misinterpretation of hematological shifts as paraneoplastic.

Conclusions: The under diagnosis of the JAK2 V617F mutation is a significant and underappreciated clinical problem in oncology. Modifying existing approaches is necessary. We propose a risk stratification algorithm whereby testing for JAK2 V617F is indicated for PC patients with splanchnic vein thromboses, persistent thrombocytosis ($>450 \times 10^9/L$) or leukocytosis ($>11 \times 10^9/L$), splenomegaly, and a relevant family history. Therapy should be revised towards a comprehensive pathogenetic approach, including preferential use of low molecular weight heparins (LMWH) over DOACs, consideration of cytoreductive therapy (hydroxycarbamide), and adjustment of supportive care (avoidance of corticosteroids). Implementing these measures will improve the efficacy of thrombosis prophylaxis and treatment, enhance quality of life, and improve oncological outcomes in this complex patient category.

Keywords: Pancreatic Cancer; Thrombosis; Venous Thromboembolic Events (VTE); JAK2 V617F Mutation; Splanchnic Vein Thrombosis; Thrombophilia; Anticoagulant Therapy; Low Molecular Weight Heparins (LMWH); Direct Oral Anticoagulants (DOAC)

Clinical Significance of the JAK2 Mutation in Oncohaematology and Oncology

Pancreatic ductal adenocarcinoma (PDAC) is notorious for its aggressive biology and dismal prognosis, carrying the highest risk of venous thromboembolic events (VTE) among all solid tumors, with a cumulative incidence exceeding 25% [1]. This prothrombotic state is multifactorial, driven by tumor-derived procogulant factors, host inflammatory responses, and therapeutic interventions. Despite the widespread adoption of thromboprophylaxis based on international guidelines, a substantial proportion of thrombotic events, particularly those involving the splanchnic venous system (portal, splenic, mesenteric veins), remain refractory to conventional anticoagulant regimens [2]. Emerging data increasingly point to a significant, yet underappreciated, contributor to this therapeutic resistance: the comorbidity of PDAC with classic Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), most notably those driven by the somatic JAK2 V617F mutation [3]. This confluence of a highly thrombogenic malignancy and a clonal hematological disorder characterized by inherent thrombophilia creates a perfect storm for catastrophic thrombotic complications.

Elucidating the Pathophysiological Role of the JAK2 V617F Mutation

The JAK2 V617F mutation represents a cornerstone in the understanding of MPN pathogenesis. It is a somatic gain-of-function mutation in exon 14 of the JAK2 gene, characterized by a guanine-to-thymine transversion, resulting in a valine-to-phenylalanine substitution at codon 617 within the pseudokinase domain [4]. This domain normally exerts autoinhibitory control over the adjacent kinase domain. The V617F substitution disrupts this autoinhibition, leading to constitutive, cytokine-independent activation of the JAK-STAT signaling pathway [5]. JAK2 is a critical tyrosine kinase for the signalling of erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor receptors. Its constitutive activation drives a clonal, multi-lineage hyper proliferation of myeloid progenitor cells, forming the pathological basis for polycythemia vera (PV), essential thrombocythaemia (ET), and primary myelofibrosis (PMF) [6]. The prevalence of this mutation is remarkably high in these conditions, being detectable in over 95% of PV cases and approximately 50-60% of ET and PMF cases [4].

The pathophysiology of thrombosis in MPNs is a complex interplay of quantitative and qualitative cellular abnormalities, extending far beyond simple blood cell counts. JAK2 V617F-positive platelets exhibit a hyperactive phenotype, demonstrating increased basal activation, enhanced aggregation responses to agonists like ADP and thrombin, and elevated surface expression of P-selectin and tis-

sue factor [7]. This creates a prothrombotic milieu where platelets are primed for activation. Furthermore, leukocytes in MPN patients are in a state of chronic, low-grade inflammation. Monocytes show increased tissue factor expression, while neutrophils demonstrate a heightened propensity to release neutrophil extracellular traps (NETosis) [8]. NETs provide a scaffold for platelet and red blood cell adhesion and activate the intrinsic pathway of coagulation, further amplifying thrombin generation. This triad of abnormal platelet, leukocyte, and red cell biology creates a sustained prothrombotic state.

The clinical significance of JAK2 V617F is particularly pronounced in the context of splanchnic vein thromboses (SVT). In patients presenting with SVT of unknown etiology (so-called “idiopathic” SVT), the prevalence of occult MPN, as signaled by the JAK2 V617F mutation, is strikingly high, ranging from 20% to 40% in various series [3, 9]. In this specific clinical scenario, the JAK2 V617F assay transcends its role as a diagnostic marker for overt MPN; it becomes a highly sensitive and specific tool for uncovering an underlying clonal hematological disorder, even in the complete absence of canonical hematological abnormalities like erythrocytosis or thrombocytosis [10]. This makes it an indispensable component of the modern diagnostic workup for SVT.

Synergistic Risks in the Comorbidity of Pancreatic Cancer and JAK2 V617F

Pancreatic cancer is a potent independent inducer of hypercoagulability through a multitude of mechanisms. Tumour cells constitutively express tissue factor, the primary initiator of the extrinsic coagulation cascade. They also release procoagulant microparticles, inflammatory cytokines (e.g., IL-1 β , TNF- α), and mucins that can directly activate platelets and endothelial cells [1, 11]. This creates a pervasive procogulant environment. When this is superimposed on the background of a JAK2 V617F-mutated MPN, the prothrombotic risk is not merely additive but likely synergistic. The constant, cytokine-independent activation of the JAK-STAT pathway in blood cells synergises with the tumor-derived prothrombotic signals, leading to an exponential increase in thrombosis risk.

Data from retrospective cohort analyses consistently demonstrate that patients with PDAC and a concomitant JAK2 V617F mutation face a dramatically elevated VTE risk, estimated to be 3 to 4 times higher than that of patients with PDAC alone [3, 11]. The thrombotic events in this comorbid population are not only more frequent but also phenotypically distinct and more aggressive. Portal vein thrombosis and other SVTs in this setting are characterized by several ominous features [3, 9, 12]:

1. **Profound Resistance to Anticoagulation:** There is a marked resistance to standard anticoagulant regimens, particularly to direct oral anticoagulants (DOACs). The efficacy of DOACs, which primarily target the final common pathway of coagulation (Factor Xa or thrombin), may be suboptimal when the primary driver of thrombosis is activated cellular elements (platelets, leukocytes) that are not directly inhibited by these drugs [11].
2. **Exceedingly High Recurrence Rates:** Despite seemingly adequate anticoagulation, the rate of recurrent thrombosis is staggering, with up to 60-70% of patients experiencing a recurrence within the first year following the initial event [3].
3. **Propensity for Disease Progression:** A significant proportion of patients with initially occult or borderline MPN will progress to overt, full-blown clinical manifestations of PV, ET, or PMF within 3 to 5 years of the index thrombotic episode [7, 12]. This underscores the JAK2 V617F mutation not only as a marker of thrombosis but also as a predictor of hematological evolution.

In summary, the JAK2 V617F mutation constitutes an independent and potent risk factor for thrombosis. Its coexistence with pancreatic cancer creates a unique clinical entity characterized by diagnostic complexity, therapeutic recalcitrance, and a dire prognosis, demanding a paradigm shift in our clinical approach.

Diagnostic Problems and Unaccounted Risks

The compelling evidence linking JAK2 V617F to refractory thromboses in pancreatic cancer stands in stark contrast to its negligible integration into routine oncological practice. The failure to systematically identify this comorbidity results in a systematic underdiagnosis of a high-risk patient cohort, leading to inadequate prophylactic strategies, suboptimal treatment, and ultimately, avoidable poor outcomes.

A Critical Analysis of Gaps in Contemporary Clinical Guidelines

A meticulous review of the positions held by leading international and national oncology bodies reveals a pervasive and conservative stance on genetic screening for thrombophilias in cancer patients. This conservatism creates significant clinical blind spots.

Organisation / Guidelines	Year	Position on JAK2 V617F Screening	Level of Evidence
NCCN (National Comprehensive Cancer Network)	2025	Does not recommend routine screening in PC patients. Considers testing only for idiopathic splanchnic vein thromboses, without specific mention of the PC context [13].	2A
ESMO (European Society for Medical Oncology)	2023	Acknowledges the association but only suggests considering testing in patients with SVT of unknown cause. Provides no specific, actionable algorithm for patients with a known underlying cancer like PC [14].	II, B
Russian Clinical Guidelines (Ministry of Health)	2025	Mention the necessity to exclude MPN in cases of persistent thrombocytosis ($>450 \times 10^9/L$) but fail to provide a concrete diagnostic pathway or address the unique challenges in oncological patients [15].	C

Table 1: Position of Clinical Guidelines on Screening for JAK2 V617F Mutation in Patients with Pancreatic Cancer.

As illustrated, none of the major guidelines endorse an active, case-finding strategy for JAK2 V617F in pancreatic cancer patients, even those presenting with clear red flags such as splanchnic vein thrombosis. This omission creates a medico-legal and clinical vacuum, where a significant proportion of comorbid pathology remains undetected until catastrophic complications occur. The guidelines' reliance on the concept of "idiopathic" or "unprovoked" SVT is particularly problematic in oncology, as it implicitly directs investigation away from the known malignancy, thereby missing the dual pathology.

Clinical Conundrums and Practical Barriers to Identifying Comorbidity

In real-world clinical practice, the identification of an occult MPN in a patient with pancreatic cancer is fraught with objective and subjective challenges that perpetuate diagnostic delays [3, 10, 12].

1. **The Masquerade of Latent MPN:** A fundamental diagnostic hurdle is the latent or oligo symptomatic phase of MPN. In up to 35% of patients with a molecularly confirmed JAK2 V617F mutation and a splanchnic thrombosis, the full blood count (FBC) at the time of the thrombotic event may be entirely unremarkable or show only borderline abnormalities [3]. A mild thrombocytosis or erythrocytosis can be easily dismissed or erroneously attributed to a paraneoplastic syndrome, post-splenectomy state, or dehydration, diverting the diagnostic focus from a primary hematological disorder.
2. **Systemic and Regional Barriers to Testing:** Access to reliable, timely, and affordable molecular genetic testing for JAK2 V617F is not universal. In many healthcare systems, including within the Russian Federation, access to high-sensitivity PCR or next-generation sequencing panels may be restricted to tertiary care centers [10, 16]. This creates a significant geographic and socioeconomic disparity in diagnostic capabilities, leading to the under-investigation of at-risk populations outside major academic institutions.
3. **Cognitive Bias in Clinical Interpretation:** Perhaps the most insidious barrier is cognitive bias. Oncologists, rightly focused on the primary cancer, often automatically attribute hematological deviations - thrombocytosis, leukocytosis, or even anemia - to the underlying malignancy (a paraneoplastic phenomenon) or to the myelosuppressive effects of chemotherapy [11, 12]. This "onco-centric" heuristic prevents the consideration of a concurrent, independent hematological disease, delaying referral to a hematologist and the initiation of a targeted diagnostic workup.

The cumulative impact of these factors is a profound diagnostic lag. Studies indicate that the diagnosis of an occult MPN in a patient with pancreatic cancer is typically delayed by 8 to 12 months after the first major thrombotic event [3, 10]. This delay is not benign; it is a period of high risk for recurrent, often fatal, thromboembolism and allows for the progression of the undiagnosed MPN, further complicating future management.

Therapeutic Dilemmas and Risks

The identification of a JAK2 V617F mutation in a patient with pancreatic cancer necessitates a fundamental reconceptualization of therapeutic strategy. It moves the clinical problem beyond simple anticoagulation and into the realm of managing a complex, multi-system comorbidity, requiring a delicate balance between thrombotic and hemorrhagic risks.

Navigating the Labyrinth of Anticoagulation Strategies

The choice of an optimal anticoagulant regimen becomes the central therapeutic dilemma, as the presence of the JAK2 V617F mutation significantly alters the risk-benefit calculus [11, 14, 17].

- **Direct Oral Anticoagulants (DOACs):** In the general oncology population with isolated VTE, DOACs like apixaban and rivaroxaban have established their efficacy and safety, offering a convenient oral alternative to low molecular weight heparin (LMWH) [14]. However, their role in the context of MPN-associated thrombosis is less clear and potentially problematic. The primary mechanism of thrombogenesis in MPN is driven by activated cellular elements—hyper-reactive platelets and pro-inflammatory leukocytes. DOACs, which target specific soluble coagulation factors (Xa or IIa), do not directly address this cellular dysregulation [11, 17]. Consequently, their efficacy in preventing thrombosis in this specific setting may be substantially attenuated, as evidenced by high recurrence rates in observational studies. Furthermore, the potential for drug-drug interactions with cytotoxics and supportive medications adds another layer of complexity.
- **Low Molecular Weight Heparins (LMWH):** LMWH (e.g., enoxaparin, dalteparin, tinzaparin) remains the cornerstone of therapy for cancer-associated thrombosis and is widely considered the preferred agent in patients with comorbid MPN [13, 18]. Their broad mechanism of action, involving the inhibition of Factor Xa and IIa and the release of tissue factor pathway inhibitor, may provide more comprehensive control over the multifaceted hypercoagulable state. In the setting of MPN and PC, the therapeutic advantage of LMWH is believed to be even more pronounced. However, management is not without challenges. In cases of extreme thrombocytosis (platelet count $>1000 \times 10^9/L$), which can occur in MPN, the risk of haemorrhagic complications may be paradoxically increased. This necessitates vigilant monitoring and may require dose adjustment (e.g., enoxaparin 1 mg/kg twice daily instead of 1.5 mg/kg once daily) to mitigate bleeding risk while maintaining antithrombotic efficacy [11, 17].

The Overlooked Impact of Supportive Therapy

The prothrombotic state induced by JAK2 V617F can be profoundly exacerbated by standard components of supportive care in oncology, creating iatrogenic risks that are frequently overlooked [11, 19].

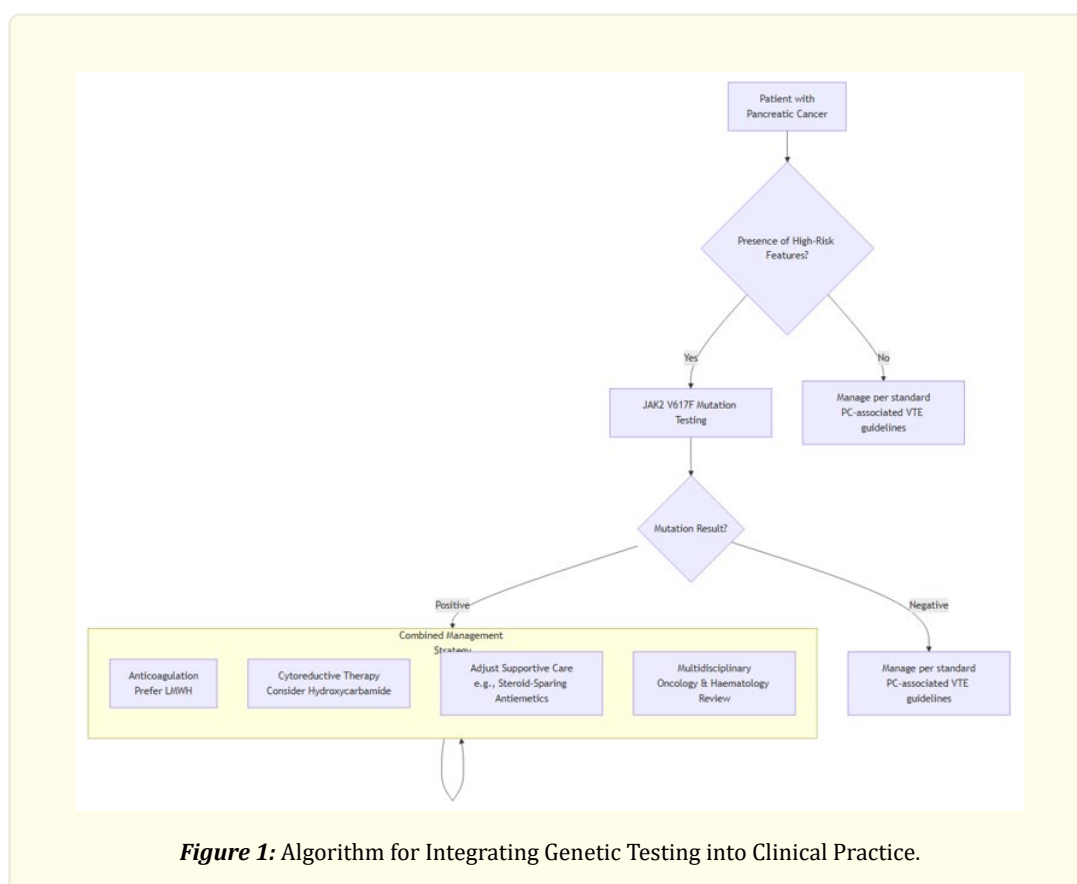
- **The Corticosteroid Conundrum:** Dexamethasone is a ubiquitous component of antiemetic prophylaxis for highly emetogenic chemotherapy regimens, including those used for pancreatic cancer. However, corticosteroids are known to exert multiple pro-thrombotic effects. They can induce a hypercoagulable state by stimulating hepatic synthesis of fibrinogen and other clotting factors, suppressing fibrinolytic activity through increased levels of plasminogen activator inhibitor-1 (PAI-1), and potentially directly stimulating megakaryopoiesis [19]. In a patient with a JAK2 V617F-mutated clone, these effects are not merely additive but may act synergistically to dramatically elevate the thrombotic risk.
- **Implementing Safer Alternatives:** For patients with proven JAK2 V617F mutation and a high VTE risk, a critical revision of supportive care is mandatory. A strategic shift towards steroid-sparing antiemetic regimens is strongly recommended. Modern protocols that leverage the synergistic effect of neurokinin-1 (NK1) receptor antagonists (e.g., aprepitant, fosaprepitant, rolapitant) and 5-HT₃ receptor antagonists (e.g., ondansetron, palonosetron) have demonstrated non-inferior efficacy to dexameth-

asone-containing regimens for preventing chemotherapy-induced nausea and vomiting, while likely conferring a significantly lower thrombotic risk [19, 20].

Therefore, the management of a pancreatic cancer patient with a JAK2 mutation demands an integrated, multidisciplinary approach that carefully orchestrates anticancer therapy, targeted anticoagulation, and meticulously reviewed supportive care to navigate the narrow therapeutic window between thrombosis and haemorrhage.

Algorithm for Integrating Genetic Testing into Clinical Practice

To bridge the identified diagnostic gaps, we propose a standardized risk stratification and management algorithm designed to be clinically implementable and cost-effective. This algorithm aims to systematically identify pancreatic cancer patients at high risk for a comorbid JAK2 V617F-mutated MPN.



Unresolved Issues and Avenues for Future Research

Despite the growing recognition of this clinical entity, numerous critical questions remain unanswered, charting a clear course for future clinical, translational, and basic science investigations.

Critical Gaps in the Contemporary Evidence Base

1. **Therapeutic Optimisation in a Evidence-Free Zone:** The most glaring deficiency is the complete absence of randomised controlled trials (RCTs) to guide antithrombotic and cytoreductive therapy in this specific patient population. Fundamental ques-

tions lack evidence-based answers [11, 17, 21]:

- a. What is the comparative efficacy and safety of LMWH versus DOACs for treating VTE in patients with solid tumours and JAK2 V617F?
 - b. What is the role and optimal timing for introducing cytoreductive agents like hydroxycarbamide? Should it be used preemptively in all JAK2-positive patients, or reserved for those with significant thrombocytosis or recurrent events?
 - c. Is there a role for JAK inhibitors (e.g., ruxolitinib) in managing refractory thrombosis in patients with active pancreatic cancer? Preliminary case reports suggest potential benefit, but their safety profile and efficacy require rigorous evaluation in clinical trials [22].
2. **Refining Diagnostic Triggers and Thresholds:** The precise haematological parameters that should mandate JAK2 V617F testing in pancreatic cancer patients are not defined [10, 15]. While persistent thrombocytosis $>450 \times 10^9/L$ is a clear indicator, many patients with occult MPN present with counts below this threshold. The diagnostic utility of other parameters—such as the degree of leukocytosis, the red cell distribution width (RDW), or the presence of a basophilia—warrants systematic investigation in large cohorts. Developing a weighted risk score that incorporates clinical and laboratory variables could enhance screening efficiency.
 3. **The Diagnostic Shadow of Cytotoxic Therapy:** Many chemotherapeutic agents used for pancreatic cancer, notably gemcitabine, cause significant bone marrow suppression [12, 23]. This can mask the characteristic haematological manifestations of an underlying MPN, such as thrombocytosis, by inducing a relative cytopenia. The diagnostic performance of the JAK2 V617F test in this setting, and the potential for “unmasking” of MPN after chemotherapy cycles, needs further study to prevent diagnostic oversight.

Promising Scientific and Translational Directions

1. **Comprehensive Molecular Profiling:** Moving beyond JAK2 V617F alone, the use of expanded next-generation sequencing (NGS) panels is a promising frontier [16, 24]. Simultaneous testing for the triple-negative MPN drivers (JAK2, CALR, MPL) alongside genes associated with hereditary cancer syndromes (e.g., BRCA1/2, PALB2, ATM) and clonal haematopoiesis of indeterminate potential (CHIP) could reveal novel associations, define patient subgroups with distinct risks, and inform personalized surveillance and management strategies. The frequency and clinical impact of such co-mutations are currently unknown.
2. **Leveraging Minimal Residual Disease and Allelic Burden Dynamics:** The use of quantitative PCR to measure the JAK2 V617F allele burden is not just a diagnostic tool but a potential powerful dynamic biomarker [5, 25]. Prospective studies are needed to determine if a high allelic burden, either at diagnosis or following tumour resection (a potential “stress test” for the mutant clone), correlates with an extreme thrombotic risk. If so, allelic burden could be used to stratify patients for more intensive prophylactic regimens, including preemptive cytoreduction. Monitoring allelic burden over time could also serve as a measure of treatment response to cytoreductive therapy.

Discussion

This comprehensive analysis substantiates the claim that the comorbidity of pancreatic cancer and JAK2 V617F-mutated myeloproliferative neoplasms is not a rare clinical curiosity but a significant, systematic, and under-addressed problem in modern oncology. The confluence of two highly prothrombotic conditions creates a perfect storm, leading to a substantial underestimation of thrombotic risk, the application of ineffectious prophylactic and therapeutic strategies, and a consequent deterioration in overall patient outcomes, including quality of life and potentially overall survival [3, 11, 12].

The central conclusion of this work is that the prevailing “onco-centric” paradigm for managing venous thromboembolism (VTE) in pancreatic cancer is fundamentally inadequate for this patient subgroup. This standard approach, largely focused on the tumour-derived hypercoagulable state, fails to integrate the critical pathophysiological contribution of the constitutively activated JAK-STAT signalling pathway and the associated cellular (platelet, leukocyte) dysregulation [5, 7]. This oversight necessitates a revision of existing clinical paradigms. It is telling that the most widely used risk assessment tool for cancer-associated thrombosis, the Khorana score,

relies solely on clinical and routine laboratory parameters and does not incorporate any genetic or molecular markers, rendering it insensitive to the risk profile of patients with MPN comorbidity [11, 14].

The clinical algorithm we propose, predicated on a combination of readily available clinical (splanchnic vein thrombosis, splenomegaly) and simple laboratory (persistent thrombocytosis/leukocytosis) criteria, is designed to be both clinically pragmatic and economically viable. Its implementation in routine practice would facilitate the systematic identification of a high-risk cohort, enabling timely referral for specialised haematological assessment and the initiation of individualized, pathophysiology-driven therapy [3, 10, 15].

From a therapeutic perspective, our analysis underscores an urgent need to transition from a simplistic model of anticoagulant monotherapy to a comprehensive, pathogenetically-oriented treatment strategy. For patients with verified comorbidity of pancreatic cancer and JAK2 V617F, the optimal management framework should be built on four pillars:

1. **Foundational Anticoagulation:** Preferential use of low molecular weight heparins (LMWH) as the cornerstone of therapy, providing broad inhibition of the coagulation cascade and potentially offering superior efficacy in this cellular-driven thrombophilia compared to DOACs [13, 18].
2. **Targeted Cyto reduction:** The timely introduction of cytoreductive therapy, such as hydroxycarbamide, to control the underlying myeloproliferative process, reduce the burden of aberrant blood cells, and mitigate the primary driver of thrombogenesis [6, 15].
3. **Adjunctive Targeted Inhibition:** Consideration of JAK inhibitors (e.g., ruxolitinib) in selected, refractory cases where standard cytoreduction is insufficient or poorly tolerated. While their use in active solid tumours requires careful study, they represent a potent tool for directly suppressing the root molecular cause of the MPN [22, 26].
4. **Meticulous Supportive Care:** A critical revision of standard supportive regimens, most notably the avoidance of corticosteroid-based antiemetics, to eliminate an iatrogenic contributor to the prothrombotic state. This should be replaced with modern, effective, steroid-sparing alternatives [19, 20].

A paramount limitation of the current analysis, and indeed the entire field, is the paucity of high-level evidence. The available literature consists predominantly of retrospective cohort studies, small case series, and expert opinion, which are inherently susceptible to bias and confounding [3, 11, 12]. This evidence gap is not merely an academic point; it directly translates to clinical uncertainty and underscores the acute and pressing need for well-designed, prospective, multi-centre observational studies and, ultimately, randomised controlled trials (RCTs). Priority areas for such research must include: precisely defining the prevalence of JAK2 V617F in consecutive cohorts of pancreatic cancer patients with and without thrombosis; rigorously evaluating the comparative effectiveness of different anticoagulant and cytoreductive strategies; and validating the prognostic utility of dynamic biomarkers like JAK2 V617F allelic burden [5, 21, 25].

Conclusion

The systematic under-recognition of the JAK2 V617F mutation in the population of patients with pancreatic cancer has grave clinical repercussions. It results in the failure of standard thromboprophylaxis, particularly with the increasingly used DOACs; leads to critical delays of 8-12 months in diagnosing an underlying myeloproliferative neoplasm; and ultimately contributes to an elevated incidence of recurrent and fatal thromboembolic events, which are often preventable [3, 10, 12]. Addressing this clinical blind spot is imperative for improving patient care.

To alter this untenable status quo, we advocate for the following concrete changes in clinical practice and research prioritization:

1. **Mandate Systematic Molecular Screening:** The JAK2 V617F test must be integrated into the standard diagnostic workup for all patients with pancreatic cancer who present with splanchnic vein thrombosis or persistent, unexplained thrombocytosis ($>450 \times 10^9/L$) or leukocytosis ($>11 \times 10^9/L$). This should be considered a standard of care for this high-risk subgroup, supported by a growing body of evidence [10, 15, 16].

2. **Adopt Pathophysiology-Driven Anticoagulation:** Upon confirmation of the JAK2 V617F mutation, the therapeutic approach must be recalibrated. Low molecular weight heparins (LMWH) in therapeutic doses should be considered the first-line agents for both treatment and secondary prophylaxis of VTE. The addition of low-dose aspirin may be considered once extreme thrombocytosis is controlled, to further target platelet hyper reactivity, though this requires careful bleeding risk assessment [11, 13, 18].
3. **Foster Compulsory Multidisciplinary Collaboration:** The management of these complex cases cannot be siloed. It demands mandatory, close, and ongoing collaboration between oncologists, hematologists, vascular medicine specialists, and surgeons. This team-based approach is essential for crafting integrated treatment plans that simultaneously address the pancreatic cancer and the myeloproliferative neoplasm [11, 15].
4. **Implement Risk-Adapted Supportive Care:** A conscious and documented effort must be made to avoid prothrombotic supportive medications, especially corticosteroids, in patients with proven JAK2 V617F mutation. Protocols should be amended to favour steroid-sparing antiemetic regimens as the preferred choice for this population [19, 20].

The implementation of these targeted measures holds the significant promise of enhancing the efficacy of thrombosis prevention and treatment, improving the quality of life, and potentially positively impacting oncological outcomes for this challenging and vulnerable cohort of patients. Future research efforts must now focus on generating the high-quality evidence needed to refine these recommendations and solidify this new standard of care.

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