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Thrombotic Risk Associated with Intravenous Mesenchymal Stromal Cell Administration: Mechanisms, Clinical Evidence, and Prevention Strategies

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Abstract

Mesenchymal Stromal Cells (MSCs) are increasingly investigated as systemic cell therapies because of their immunomodulatory, anti-inflammatory, and regenerative properties. Although Intravenous (IV) administration is convenient and widely used, direct exposure of MSCs to circulating blood raises concerns regarding coagulation activation, pulmonary microvascular obstruction, and thromboembolic complications. MSCs can express Tissue Factor (TF/CD142), expose procoagulant Phosphatidylserine (PS), and interact with coagulation, complement, platelets, and innate immune pathways. Their relatively large size also promotes initial pulmonary retention following IV infusion. These biological effects are influenced by tissue source, donor characteristics, culture and expansion conditions, cryopreservation and post-thaw handling, cell viability and aggregation, dose, concentration, and administration conditions.

Clinically significant thrombotic complications have been reported, and transient or subclinical coagulation activation may occur without overt thrombosis. However, controlled clinical trials and systematic reviews have not demonstrated a consistent increase in clinically significant thrombotic or thromboembolic events following intravascular MSC administration. These findings indicate that procoagulant potential, subclinical coagulation activation, and clinically manifest thrombosis are related but distinct outcomes. TF/CD142 is an important mechanistic and product-related risk attribute but is insufficient as a stand-alone predictor of clinical thrombotic risk.

A comprehensive patient-product-administration risk-based approach integrating patient-specific thrombotic susceptibility, product characterization, functional hemocompatibility assessment, product-specific dose and administration procedures, and appropriate peri-infusion monitoring may provide a more rational framework for risk mitigation. This review summarizes the mechanisms underlying thrombotic and microembolic risks associated with IV MSC administration, evaluates the available clinical evidence, and discusses current and emerging strategies for safer systemic MSC therapy.

Keywords: Mesenchymal stromal cells; Intravenous administration; Thrombosis; Tissue factor; Coagulation; Hemocompatibility

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Introduction

Mesenchymal Stromal Cells (MSCs) have emerged as a promising cellular therapeutic platform because of their immunomodulatory, anti-inflammatory, trophic, and tissue-reparative properties. MSCs derived from bone marrow, adipose tissue, umbilical cord, placenta, and other tissues have been investigated across a wide range of clinical conditions. Among the various routes of administration, Intravenous (IV) infusion is frequently employed because it is minimally invasive, technically straightforward, and enables systemic delivery of cells [1,2].

Clinical experience accumulated over the past two decades has generally supported a favorable safety profile for MSC administration. An early systematic review and meta-analysis found no clear association between MSC therapy and major acute toxicities, organ complications, infection, malignancy, or mortality, although transient fever occurred more frequently following MSC administration [3]. More recently, a systematic review and meta-analysis of 42 randomized controlled trials involving 2,280 patients receiving intravascular Umbilical Cord-Derived MSCs (UC-MSCs) similarly found no significant signal of harm for thrombotic or thromboembolic events [4].

Despite this generally reassuring clinical experience, IV MSC administration presents biological and physiological challenges distinct from those of conventional soluble therapeutics. MSCs are relatively large living cells, and a substantial proportion are initially retained within the pulmonary circulation following IV administration, a phenomenon commonly referred to as the pulmonary first-pass effect [5]. Although pulmonary retention itself should not be equated with thromboembolism, excessive cellular accumulation, aggregation, or accompanying coagulation activation may contribute to microvascular obstruction under certain conditions.

MSCs can also express tissue factor (TF/CD142), the principal initiator of the extrinsic coagulation pathway. Exposure of TF-expressing MSCs to circulating blood can promote factor VII/VIIa binding, factor X activation, thrombin generation, and fibrin formation [6-8]. Importantly, TF expression and functional procoagulant activity vary considerably among MSC products according to tissue source, donor characteristics, and manufacturing conditions [6,8-11].

MSC-blood interactions extend beyond TF alone. Exposure to blood may initiate an Instant Blood-Mediated Inflammatory Reaction (IBMIR) involving interconnected activation of coagulation, complement, platelets, and innate immune pathways [7,10]. Platelet interactions may vary among MSC populations, while phosphatidylserine exposure, cell viability, aggregation, culture conditions, cryopreservation and post-thaw handling, cell dose, and concentration may further modify hemocompatibility [10,12-14]. Thus, the thrombotic potential of an MSC product is likely to reflect multiple interacting biological and product-related determinants rather than a single marker.

Recipient characteristics may further modify the clinical consequences of these interactions. Malignancy, systemic inflammation, cardiovascular disease, pre-existing coagulation abnormalities, and baseline venous thromboembolism risk may increase susceptibility to thrombosis [10,15]. Patient- and product-related determinants may also interact, particularly in autologous therapy, where underlying disease may influence the hemostatic phenotype of the manufactured cellular product [16].

Importantly, biological procoagulant potential does not necessarily translate into clinically apparent thrombosis. Serious thromboembolic complications following IV cell administration have been documented in individual reports [17,18] whereas controlled clinical trials and systematic reviews have not demonstrated a consistent increase in clinically significant thromboembolic events following appropriately administered MSC therapy [3,4]. This apparent discrepancy highlights the importance of distinguishing procoagulant potential, subclinical coagulation activation, pulmonary cell trapping or microvascular obstruction, and clinically manifest thromboembolism.

Accordingly, thrombotic risk assessment for IV MSC therapy should extend beyond a single biomarker. TF/CD142 remains an important mechanistic and product-related risk attribute, but assessment of the final product should also consider functional hemocompatibility, manufacturing and formulation characteristics, administration conditions, and patient-specific thrombotic susceptibility [10,12]. Recent recommendations have similarly emphasized standardized cell handling, patient assessment, administration procedures, and peri-infusion monitoring as components of safer IV MSC therapy [19].

This review summarizes the mechanisms underlying thrombotic and microembolic risks associated with IV MSC administration, evaluates MSC- and product-related determinants and the available clinical evidence, and discusses patient-related risk factors and current risk-mitigation strategies. By integrating mechanistic, translational, and clinical evidence, we propose a patient-product-administration framework for interpreting thrombotic risk and improving the safety of systemic MSC therapy.

Relevant literature was identified through searches of PubMed using combinations of terms related to mesenchymal stromal cells, intravenous administration, thrombosis, thromboembolism, tissue factor/CD142, coagulation, hemocompatibility, IBMIR, platelet interactions, and pulmonary embolism. Mechanistic, translational, clinical, and systematic-review evidence relevant to thrombotic risk associated with intravascular MSC administration was considered, with particular attention to recent clinical safety evidence.

Mechanisms Underlying Thrombotic Risk

The thrombotic risk associated with IV MSC administration is likely to arise from several interconnected mechanisms rather than a single procoagulant pathway. These include TF/CD142-mediated coagulation, exposure of procoagulant phospholipids such as Phosphatidylserine (PS), platelet interactions, activation of the Instant Blood-Mediated Inflammatory Reaction (IBMIR), and mechanical interactions between infused cells and the pulmonary microvasculature. Their relative contributions may vary according to product characteristics, manufacturing, cellular exposure, administration conditions, and recipient thrombotic and inflammatory status [7,10,12,20].

Tissue factor/CD142-mediated activation of coagulation

TF, also known as CD142 or coagulation factor III, is the principal physiological initiator of the extrinsic coagulation pathway. IV administration introduces TF-expressing MSCs directly into circulating blood, allowing cell-surface TF to interact with factor VII/VIIa. Formation of the TF-FVIIa complex activates factors IX and X, leading to factor Xa generation, prothrombinase complex formation, thrombin generation, and ultimately fibrin formation [6-8].

The importance of TF in MSC-associated coagulation has been demonstrated experimentally. Tatsumi, et al. [8] identified TF as a major contributor to coagulation activation and thromboembolism following IV MSC administration. Subsequent studies demonstrated substantial variation in TF expression and functional procoagulant activity among MSC preparations. Adipose-derived MSCs have shown greater procoagulant activity than BM-MSCs in some

comparisons, while considerable donor variability has been observed even within BM-derived products [6]. Source-dependent differences have also been demonstrated among BM-, adipose-, umbilical cord-, placental-, and other stromal cell products [9,11,21].

Experimental manipulation further supports a direct mechanistic role for TF. Selection of TF-deficient stromal cell populations improved hemocompatibility [21], while TF knockout or silencing reduced procoagulant activity, platelet aggregation, or thrombotic effects without substantially compromising key MSC characteristics [22,23].

However, TF expression should not be interpreted as a stand-alone predictor of clinical thrombosis. TF levels can vary with cell density, hypoxia, inflammatory conditions, and other manufacturing variables, and clinical studies have not established a direct correlation between TF expression and post-infusion thrombotic events or coagulation biomarkers [24]. TF/CD142 should therefore be considered an important mechanistic and product-related risk attribute within a broader assessment of hemocompatibility [12].

Phosphatidylserine and additional procoagulant surface features

TF is not the only cellular determinant capable of promoting coagulation. PS is normally localized predominantly to the inner leaflet of the plasma membrane but becomes externalized during cellular activation, stress, apoptosis, or membrane injury. Externalized PS provides a negatively charged phospholipid surface that supports assembly of coagulation enzyme complexes, including tenase and prothrombinase, thereby accelerating thrombin generation [25,26].

MSC manufacturing and handling may influence PS exposure through cellular stress associated with culture, harvesting, cryopreservation, thawing, or loss of membrane integrity. Silachev, et al. [25] demonstrated that human UC-MSCs and their extracellular vesicles exhibited procoagulant activity associated with both TF and PS-positive membrane surfaces. MSC-derived extracellular vesicles may similarly carry TF and expose PS, further illustrating the potential contribution of membrane-derived structures to coagulation [25,26].

Thus, the procoagulant phenotype of an MSC product reflects not only TF expression but also membrane phospholipid composition, cellular integrity, and other pro- and anticoagulant properties.

Platelet interactions, IBMIR, and thromboinflammation

Following IV administration, MSCs immediately encounter blood and may trigger IBMIR, an interconnected response involving coagulation, complement, platelets, leukocytes, and inflammatory mediators [7,10].

MSC-platelet interactions appear to depend on tissue source and cellular phenotype. Podoplanin (PDPN) can promote platelet interactions through the platelet receptor CLEC-2, providing a TF-independent mechanism of platelet activation and platelet-rich aggregate formation in some MSC populations [14,27]. Conversely, MSCs can inhibit platelet activation and aggregation through CD73-mediated adenosine generation [13]. The net platelet response may therefore reflect the balance between activating and inhibitory pathways rather than a uniformly prothrombotic MSC phenotype.

Coagulation and complement provide additional interacting components of IBMIR. MSC exposure to blood can activate complement, resulting in complement deposition on cellular surfaces, generation of activation products, and interactions with complement receptor-bearing innate immune cells [28]. Thrombin, complement-derived mediators such as C3a and C5a, activated platelets, and leukocytes can subsequently reinforce inflammatory and coagulation responses, contributing to thromboinflammation [7,28].

Blood contact may also induce rapid MSC injury, lysis, and phenotypic changes, potentially altering subsequent interactions with coagulation and innate immune pathways [29]. The intensity of these interactions varies among MSC products and may be influenced by dose, donor, passage, and cryopreservation [7,30].

Together, these observations indicate that MSC-blood interactions represent a dynamic process involving coagulation, complement, platelets, innate immunity, and cellular injury. Functional hemocompatibility may therefore provide information not captured by conventional MSC identity and viability criteria alone [12].

Pulmonary first-pass effect and mechanical microvascular obstruction

In addition to biochemical coagulation activation, IV-administered MSCs encounter mechanical constraints within the pulmonary circulation. Because MSCs are relatively large, a substantial proportion is initially retained within the lung microvasculature after peripheral IV infusion, producing the pulmonary first-pass effect [5,31,32]. Pulmonary retention may also be influenced by culture-dependent changes in adhesion molecules and other cellular properties [33].

Importantly, pulmonary retention should not be considered synonymous with pulmonary thromboembolism. Pulmonary cell trapping primarily reflects biodistribution and mechanical interaction with the microvasculature, whereas thromboembolism involves pathological vascular obstruction associated with thrombotic material. Nevertheless, these processes may interact. High cell concentrations, aggregation, reduced deformability, or enhanced adhesion may increase mechanical obstruction, while TF-mediated coagulation and platelet activation may promote local thrombus formation around retained cells [5,8,14,21,34].

Experimental studies support this potential convergence. Liao, et al. [34] demonstrated dose-dependent coagulation abnormalities and pulmonary thrombotic complications following IV BMSC administration, with TF implicated as a major mediator. However, early pulmonary accumulation itself is a common biodistribution phenomenon and should not be interpreted as evidence of pathological embolism.

Thus, thrombotic and microembolic risk following IV MSC administration is best conceptualized as the potential convergence of biochemical coagulation activation, platelet and inflammatory blood interactions, and mechanical pulmonary microvascular effects. The magnitude and clinical significance of these responses depend on the characteristics of the cellular product, administration conditions, and recipient susceptibility.

MSC-Related determinants of thrombogenicity

The thrombogenic potential of MSCs is not an invariant property of the cell type but rather a product-specific phenotype influenced by tissue origin, donor characteristics, culture and expansion conditions, cryopreservation and post-thaw handling, cell dose and concentration, and the physical state of the final cell suspension. These variables may alter TF/CD142 expression, membrane integrity,

Table 1: Major MSC- and Product-Related Determinants of Thrombogenicity Following Intravenous Administration.

Determinant	Potential effect on thrombogenicity	Proposed mechanism / relevant characteristics	Practical implication for IV MSC therapy	Key refs.
Tissue source	Variable; relatively higher procoagulant activity has been reported for some adipose- and perinatal-derived products than for BM-MSCs	Source-dependent differences in TF/CD142 expression and activity; differences in platelet-interacting phenotype and overall hemocompatibility	Tissue source provides useful context but should not be used alone to predict thrombogenicity; characterize the final product	[6,11,14,24]
Donor characteristics	Variable between donors, including within the same tissue source	Inter-donor variation in TF expression, cellular phenotype, and functional coagulation responses; underlying disease may alter cellular hemostatic properties	Consider donor- and batch-specific variability when evaluating intravascular safety	[6,16,24]
Culture and expansion conditions	May increase or modify procoagulant phenotype	Cell density, passage, hypoxia, inflammatory exposure, and other culture conditions may alter TF/CD142 and related blood-interacting phenotypes	Hemocompatibility should be assessed after the clinically relevant manufacturing process, not inferred from starting tissue	[6,10,24]
Cryopreservation and post-thaw handling	May increase procoagulant interactions when cellular integrity is impaired	Membrane injury, PS exposure, reduced viability/recovery, cellular debris, and altered surface phenotype after thawing	Characterize the actual post-thaw product under conditions representative of clinical administration	[30,35,36]
Cell viability and membrane integrity	Reduced integrity may increase procoagulant surface exposure	Membrane disruption and externalization of PS can provide a catalytic surface for coagulation reactions	Conventional viability testing should be interpreted together with membrane integrity and functional hemocompatibility	[25,26,35]
Cell aggregation / suspension quality	Increased aggregation may increase microvascular obstruction and potentially enhance local coagulation	Increased effective particle size, pulmonary microvascular retention, cell–cell interactions, and localized blood–cell contact	Confirm uniform cell suspension and absence of clinically relevant aggregates before administration	[5,31,33]
TF/CD142 expression and activity	Higher TF generally associated with greater experimental procoagulant activity	TF–FVII/FVIIa complex initiates extrinsic coagulation and promotes FX activation and thrombin generation	Important risk-associated product attribute, but no universally validated TF threshold predicts clinical thrombosis	[6,8,11,20-24]
PS exposure	Increased PS may enhance coagulation reactions	Externalized PS provides a negatively charged phospholipid surface supporting coagulation enzyme complexes and thrombin generation	Consider as a complementary marker of cellular procoagulant state and membrane quality	[25,26]
Platelet-interacting phenotype	May enhance or, under some conditions, modulate platelet activation	Interactions involving PDPN-CLEC-2 and other platelet-regulatory pathways; effects may vary among MSC populations	Platelet interactions represent a distinct component of hemocompatibility beyond TF alone	[13,14,27]
Total cell dose	Higher exposure may increase coagulation activation and pulmonary cellular burden	Greater number of blood–cell interactions. Dose-dependent coagulation activation and microvascular effects	Establish a product-specific clinically justified dose rather than assuming a universal safe dose	[6,24,37,38]
Cell concentration / formulation	High concentration may increase local cellular and microvascular burden	Increased cell–cell contact, aggregation potential, and high local exposure during infusion	Optimize concentration, formulation, and infusion conditions; dose and concentration should be considered separately	[10,19,24,36]
Final product hemocompatibility	Integrates multiple determinants and may better reflect actual intravascular behavior	Combined effects of TF activity, PS exposure, thrombin/FXa generation, platelet interactions, viability, aggregation, and manufacturing history	Functional testing of the final formulated product may provide more informative risk characterization than any single marker	[9,12,24,47]

Abbreviations: BM-MSC: Bone Marrow-Derived Mesenchymal Stromal Cell; CLEC-2: C-Type Lectin-Like Receptor 2; FVII/FVIIa: Factor VII/Activated Factor VII; FX: Factor X; IV: Intravenous; MSC: Mesenchymal Stromal Cell; PDPN: Podoplanin; PS: Phosphatidylserine; TF: Tissue Factor.

Phosphatidylserine (PS) exposure, platelet interactions, cell viability, aggregation, and functional interactions with the coagulation system [6,7,12,15,24]. The major MSC- and product-related determinants and their practical implications for IV administration are summarized in Table 1.

Tissue source

Tissue origin is one of the most extensively investigated determinants of MSC-associated procoagulant activity. MSCs derived from bone marrow, adipose tissue, umbilical cord, placenta, and other tissues may differ substantially in TF/CD142 expression, platelet interactions, and functional hemocompatibility [6,9-12,14,21,24]. BM-MSCs have generally demonstrated relatively low TF expression compared with MSCs derived from adipose or some perinatal tissues. Direct comparative studies have confirmed source-dependent differences in TF expression, coagulation activity, and clot formation, while also demonstrating considerable donor-dependent variability [6,9,21].

Perinatal stromal cells provide additional evidence of source-dependent heterogeneity. Placental decidua-derived stromal cells have demonstrated greater TF-associated procoagulant activity than BM-MSCs, while platelet interactions may also vary among MSC populations according to expression of molecules such as podoplanin [11,14]. The functional importance of TF is further supported by studies showing improved hemocompatibility following selection of TF-deficient stromal populations or genetic TF reduction [21,22].

However, tissue source is not an absolute predictor of thrombogenicity. TF expression can be modified by cell density, hypoxia, inflammatory conditions, and other manufacturing variables, resulting in substantial variability even within the same tissue-source category [24]. Tissue origin should therefore be

regarded as an initial indicator of potential hemocompatibility rather than a sufficient predictor of clinical thrombotic risk.

Donor, patient, culture conditions, and passage

Substantial differences in procoagulant activity can occur among MSC preparations derived from the same tissue. Donor-dependent variability in MSC-blood interactions and coagulation activity has been demonstrated experimentally [6,7]. In autologous therapy, underlying disease may further influence the hemostatic phenotype of the cellular product. For example, adipose-derived MSCs isolated from patients with type 2 diabetes showed reduced fibrinolytic activity in the context of peripheral microthrombotic events, suggesting that patient- and product-related risk may not always be independent [16].

Ex vivo expansion can further modify hemocompatibility. Passage, cell density, oxygen tension, inflammatory stimulation, media composition, and harvesting procedures may alter TF expression and other properties relevant to coagulation [6,7,24]. Expansion-associated changes in adhesion molecules may also influence pulmonary entrapment following systemic administration [33]. These findings are particularly relevant when inflammatory priming or other manufacturing modifications are introduced to enhance MSC potency, because improved therapeutic activity cannot be assumed to preserve hemocompatibility.

Cryopreservation, thawing, and post-thaw handling

Cryopreservation enables centralized manufacturing and off-the-shelf clinical use but may alter membrane integrity, metabolism, viability, surface phenotype, and blood interactions [35]. Cellular stress or apoptosis can increase exposure of procoagulant phospholipids such as PS, while damaged cells, debris, and aggregates may affect both hemocompatibility and pulmonary microvascular passage [25,35].

Direct comparisons of fresh and freeze-thawed MSCs have demonstrated altered blood and complement interactions following cryopreservation [30]. Post-thaw formulation and handling can further influence cell recovery and stability [36]. Thus, the condition of the product at the time of administration may differ substantially from that measured before cryopreservation. Post-thaw viability, recovery, suspension stability, holding time, and aggregation should therefore be considered together rather than relying on a single viability measurement.

Cell dose and concentration

Cell dose is a biologically plausible determinant of coagulation activation because increasing numbers of MSCs increase the amount of TF- and PS-bearing cellular surface exposed to circulating blood. Experimental studies have demonstrated dose-dependent coagulation responses and, at higher exposure, pulmonary thrombotic abnormalities following systemic MSC administration [7,21,34,37].

Dose-related coagulation activation has also been demonstrated in humans. In healthy volunteers receiving escalating doses of IV adipose-derived MSCs, Perlee, et al. [38] observed dose-dependent increases in coagulation and fibrinolytic markers, including thrombin-antithrombin complexes and D-dimer, without clinically apparent thromboembolism. This distinction is important: dose-dependent biological coagulation activation should not be interpreted as equivalent to clinically manifest thrombosis.

No universal safe IV MSC dose can currently be defined because the relationship between dose and clinical outcome is influenced by cell source, TF phenotype, manufacturing process, recipient characteristics, and other factors. Cell concentration should also be distinguished from total dose. The same total number of cells can be administered at different concentrations, potentially altering cell-cell interactions, aggregation, and local cellular exposure during infusion [36]. Dose and concentration should therefore be considered together with formulation and administration conditions.

Cell viability, aggregation, and suspension quality

Percentage viability alone provides an incomplete description of an MSC product intended for IV administration. Preparations with similar viability may differ in apoptotic-cell burden, membrane integrity, PS exposure, cellular debris, cell-size distribution, and aggregate formation. Experimental evidence demonstrating PS-associated procoagulant activity in MSCs and MSC-derived membrane particles further supports the importance of membrane quality beyond conventional viability testing [25].

Aggregation is particularly relevant because IV MSCs already undergo substantial pulmonary first-pass retention [5,31,33]. Aggregates increase effective particle size and may enhance mechanical microvascular obstruction, while accumulation of TF-bearing or platelet-interacting cells may create a local environment favorable to coagulation and platelet activation [14]. Suspension quality and homogeneity should therefore be considered as part of final-product assessment.

Collectively, these findings support a multidimensional concept of MSC thrombogenicity. Tissue origin establishes part of the baseline phenotype, but donor characteristics, manufacturing, cryopreservation, post-thaw handling, dose, concentration, viability, and aggregation modify the final interaction with circulating blood. Accordingly, thrombogenic risk should be regarded primarily as a property of the final product–administration combination, rather than as a uniform intrinsic characteristic of MSCs.

Clinical Evidence of Thrombotic and Embolic Events

Although experimental studies demonstrate that MSCs can activate coagulation and interact with the pulmonary microvasculature, the clinical significance of these findings remains less clearly defined. Available evidence ranges from isolated reports of overt thromboembolic complications to transient coagulation biomarker changes and controlled clinical trials in which clinically significant thrombotic events appear uncommon. These forms of evidence address distinct aspects of risk and should not be interpreted interchangeably. The principal clinical evidence is summarized in Table 2.

Reported clinical thromboembolic events

Clinically apparent thrombotic complications following intravascular MSC-related cell administration have been reported. Jung et al. [17] described multiple pulmonary emboli following repeated IV administration of autologous adipose-derived cellular products in three related individuals, including pulmonary infarction and elevated D-dimer in the symptomatic index patient. However, the intervention was performed outside a conventional controlled MSC trial, and detailed information regarding manufacturing, TF/CD142 expression, cell concentration, aggregation, infusion conditions, and hemocompatibility was unavailable. The report therefore establishes a temporal association but does not identify the mechanism or

Table 2: Clinical Evidence Relevant to Thrombotic Risk Following Intravenous or Intravascular MSC Administration.

Clinical evidence	Population/Study design	MSC product/ administration	Main thrombotic or coagulation-related findings	Clinical interpretation	Key refs.
Clinically apparent thrombotic events					
Pulmonary embolism after repeated IV cell administration	Case report; 3 related individuals	Autologous adipose-derived cellular product; repeated IV administration	Multiple pulmonary emboli after repeated administration; pulmonary infarction and elevated D-dimer in the symptomatic index patient	Demonstrates that clinically apparent pulmonary thromboembolism can occur after repeated IV cellular therapy; causality and product-specific mechanisms remain uncertain because manufacturing, TF/CD142, aggregation, and hemocompatibility characteristics were incompletely defined	[17]
Peripheral venous thrombosis following IV UC-MSC infusion	Two case reports; patients with renal disease	UC-MSCs; peripheral IV infusion	Symptomatic venous thrombosis in the infused upper extremity near the puncture/infusion site	Demonstrates venous thrombosis temporally associated with IV UC-MSC infusion; patient- and procedure-related factors may have contributed	[18]
Peripheral microthrombotic events associated with autologous cell therapy	Clinical observation with mechanistic investigation; patients with type 2 diabetes and critical limb ischemia	Autologous AD-MSCs; intravascular cell therapy	Peripheral microthrombotic events in two patients; diabetes-derived AD-MSCs subsequently showed reduced fibrinolytic activity	Suggests that underlying disease may influence both recipient thrombotic susceptibility and the hemostatic phenotype of an autologous cell product	[16]
Subclinical or transient coagulation activation					
Dose-dependent coagulation activation without overt thrombosis	Randomized, placebo-controlled human experimental study; healthy volunteers	Allogeneic AD-MSCs; escalating-dose IV administration	Dose-dependent activation of coagulation and fibrinolysis, including increased TAT complexes and D-dimer at higher cellular exposure; no clinically apparent thromboembolism	Demonstrates that biological coagulation activation can occur without overt clinical thrombosis and may depend on cellular exposure	[38]
Transient coagulation activation following IV UC-MSC administration	Clinical IV MSC study	UC-MSCs; IV administration	Transient elevation of D-dimer following IV administration without clinically apparent thrombosis	Supports the distinction between subclinical coagulation activation and clinically manifest thrombotic events	[24]
Controlled and aggregated clinical safety evidence					
Early systematic evidence of overall MSC safety	Systematic review/ meta-analysis; 36 prospective studies, 1,012 participants	Intravascular MSC administration across multiple cell sources and indications	No significant association with major acute toxicity or organ complications; transient fever increased	Supports a generally favorable clinical safety profile; thrombotic outcomes were not the primary focus of many included studies	[3]
No significant increase in thrombotic or embolic events in randomized trials	Systematic review/ meta-analysis; 55 RCTs, 2,696 participants	Intravascular MSC administration	No significant increase in thrombotic or embolic events versus control (RR 1.14, 95% CI 0.67–1.95)	Larger randomized evidence does not demonstrate a consistent increase in clinical thrombotic or embolic events; uncommon events and trial heterogeneity limit precision	[40]
No significant thrombotic safety signal with intravascular UC-MSCs	Systematic review/ meta-analysis; 42 RCTs, 2,280 adults	Intravascular UC-MSC administration	No significant harm signal for thrombotic or thromboembolic events; fever increased	Recent randomized evidence supports the absence of a consistent clinical thrombotic signal, while not excluding uncommon events or product-specific risk	[4]

Abbreviations: AD-MSC: Adipose-Derived Mesenchymal Stromal Cell; CI: Confidence Interval; IV: Intravenous; MSC: Mesenchymal Stromal Cell; RCT: Randomized Controlled Trial; RR: Risk Ratio; TAT: Thrombin-Antithrombin; TF: Tissue Factor; UC-MSC: Umbilical Cord-Derived Mesenchymal Stromal Cell.

determine causality.

Wu, et al. [18] subsequently reported symptomatic peripheral venous thrombosis in two patients following IV UC-MSC infusion, with thrombi identified near the infusion site. Acosta et al. [16] reported peripheral microthrombotic events in patients receiving autologous adipose-derived cell therapy and subsequently demonstrated reduced fibrinolytic activity in MSCs derived from patients with type 2 diabetes. The latter observation raises the possibility that underlying disease may influence both recipient thrombotic susceptibility and the hemostatic phenotype of an autologous cell product.

Collectively, these reports demonstrate that clinically significant thrombotic events following intravascular cell administration are possible. However, case reports and small observational studies cannot establish incidence or causality, and their interpretation is complicated by patient risk factors, product characteristics, dose, repeated administration, and infusion procedures.

Subclinical coagulation activation

Coagulation activation may occur without clinically apparent thrombosis. In a controlled study of healthy volunteers, Perlee et al. [38] demonstrated dose-dependent increases in coagulation and fibrinolytic markers following escalating doses of IV adipose-derived MSCs, including increases in thrombin-antithrombin complexes and D-dimer at the highest dose, without clinically apparent thromboembolism.

Similarly, Hoang et al. [24] observed a transient increase in D-dimer following IV UC-MSC administration, whereas comparable

changes were not observed following intrathecal administration. TF expression did not correlate with the measured coagulation indicators. Other intravascular stromal cell studies have also documented infusion-associated coagulation responses and explored pharmacological strategies to attenuate them [39].

These observations demonstrate that biological coagulation activation and clinically manifest thrombosis are related but distinct outcomes. Whether the magnitude or persistence of post-infusion biomarker changes predicts subsequent clinical thrombosis remains unknown.

Evidence from controlled trials and systematic reviews

The isolated thrombotic events described above should be interpreted in the context of the substantially larger controlled clinical literature. The safe cell systematic review evaluated 36 prospective studies involving 1,012 participants and found an overall favorable safety profile for intravascular MSC administration, although thrombotic outcomes were not the principal focus of many included studies [3].

Subsequent evidence has more directly addressed thrombotic risk. Thompson, et al. [40] analyzed 55 randomized controlled trials involving 2,696 participants and found no significant increase in thrombotic or embolic events following intravascular MSC administration compared with controls (RR 1.14, 95% CI 0.67-1.95). More recently, Hum et al. [4] analyzed 42 randomized controlled trials comprising 2,280 adults receiving intravascular UC-MSCs and similarly found no significant harm signal for thrombotic or thromboembolic events.

Additional clinical studies across different MSC sources and indications have broadened the available safety experience. These include clinical trials of BM-MSCs in idiopathic pulmonary fibrosis, adipose-derived MSCs in COVID-19, UC-MSCs in ischemic stroke, and placenta-derived adherent stromal cells in Crohn's disease, together with broader preclinical and clinical safety evaluation of intravenously administered adipose-derived MSCs [41-45]. Although these studies were generally not designed or powered specifically to determine thrombotic risk, they extend the safety experience across different products, doses, administration schedules, and patient populations.

Taken together, controlled clinical studies and successive systematic reviews indicate that clinically significant thrombotic or thromboembolic events are uncommon and have not emerged as a consistent safety signal following intravascular MSC administration under controlled clinical conditions [3,4,40-45].

Nevertheless, these findings do not establish the absence of risk. Thrombotic events are relatively uncommon, many individual trials were not powered specifically for VTE or pulmonary embolism, and substantial heterogeneity exists in MSC source, manufacturing, dose, administration, concomitant therapies, thromboprophylaxis, and adverse-event surveillance. The absence of a statistically significant signal should therefore not be interpreted as evidence that biological thrombotic risk is absent.

Reconciling mechanistic and clinical evidence

The apparent discrepancy between experimental thrombogenicity and the generally favorable clinical safety record is central to the interpretation of IV MSC therapy. Experimental evidence demonstrates that MSCs can express TF, expose PS, generate thrombin, interact with platelets, activate IBMIR, and become retained within the pulmonary microvasculature [5-14,25-28,31,33,34]. Clinically apparent thrombotic events have also been reported, yet controlled clinical evidence has not demonstrated a consistent increase in clinically significant thrombosis [3,4,16-18,40-45].

Several factors may explain this difference. MSC-associated coagulation activity varies among products, and standardized manufacturing, product release testing, administration procedures, patient selection, and monitoring may reduce clinical risk. Furthermore, transient coagulation activation does not necessarily progress to thrombosis, particularly when endogenous anticoagulant and fibrinolytic mechanisms remain sufficient. Recipient characteristics may further modify the clinical consequences of the same MSC product.

Current evidence therefore supports a nuanced interpretation: IV MSC administration has a biologically plausible and experimentally demonstrated procoagulant potential, and clinically significant thrombotic events can occur; however, these events appear uncommon and have not emerged as a consistent safety signal in controlled clinical trials.

The key clinical question is therefore not simply whether MSCs are procoagulant, but which combinations of product characteristics, administration conditions, and patient susceptibility convert biological procoagulant potential into clinically meaningful thrombotic risk.

Patient-related risk factors

The clinical consequences of MSC-associated coagulation activation are likely to depend not only on the characteristics of the administered cellular product but also on the recipient's baseline thrombotic, inflammatory, and hemostatic status. This is particularly relevant because many diseases targeted by systemic MSC therapy-including severe inflammatory disorders, malignancy, cardiovascular disease, and critical illness-are themselves associated with increased thrombotic risk [15,19,46]. Patient-related factors should therefore be considered together with product thrombogenicity and administration-related variables.

Pre-existing thrombotic risk and coagulation abnormalities

A history of Venous Thromboembolism (VTE), active or recent thrombosis, known thrombophilia, and pre-existing coagulation abnormalities should be considered when evaluating patients for IV MSC administration. Previous VTE is an established predictor of subsequent thrombotic risk and is incorporated into conventional clinical VTE risk-assessment models [46].

In a patient with an already prothrombotic hemostatic environment, additional coagulation activation induced by MSC-blood interactions could theoretically have greater clinical consequences than the same biological stimulus in a lower-risk recipient. This does not imply that previous VTE or coagulation abnormalities represent absolute contraindications to MSC therapy, but rather supports individualized benefit-risk assessment.

Baseline abnormalities may also complicate interpretation of post-infusion biomarkers. Transient increases in D-dimer and other coagulation or fibrinolytic markers have been observed following IV MSC administration without clinically apparent thrombosis [24,38]. Such changes may be more difficult to interpret in patients with pre-existing hypercoagulability or elevated baseline D-dimer.

Pre-infusion assessment should therefore establish relevant thrombotic history and current clinical status. Conventional coagulation testing and additional biomarkers may be considered when clinically appropriate, although no MSC-specific laboratory panel or validated threshold currently predicts post-infusion thrombosis [12,19,24].

Systemic inflammation and hypercoagulable states

Inflammation and coagulation are closely interconnected. Systemic inflammation can promote endothelial activation, TF expression, platelet activation, and dysregulation of anticoagulant and fibrinolytic pathways, thereby shifting the hemostatic balance toward thrombosis.

This issue became particularly evident during the development of MSC therapies for severe COVID-19, in which critically ill patients frequently exhibited substantial hypercoagulability and thromboinflammation. Moll et al. [15] cautioned that poorly characterized MSC products with high TF/CD142 activity could provide an additional procoagulant stimulus in such vulnerable recipients. The principle extends beyond COVID-19 because chronic inflammatory disorders, active infection, and other systemic inflammatory conditions are recognized contributors to VTE risk [46].

Systemic inflammation may also interact with product characteristics because inflammatory stimulation can modify MSC TF expression and other properties relevant to hemocompatibility [24]. However, no validated inflammatory biomarker threshold currently defines when IV MSC administration should be withheld. Systemic inflammation should therefore be considered within an integrated risk assessment rather than as an isolated contraindication.

Malignancy, immobility, and other clinical risk factors

Several characteristics commonly encountered in patients considered for systemic cell therapy are independently associated with VTE, including active malignancy, prolonged immobility, advanced age, previous VTE, and selected cardiovascular or systemic conditions [46]. These factors frequently coexist and may cumulatively increase baseline thrombotic risk.

However, current evidence does not establish MSC-specific exclusion thresholds for age, malignancy, mobility status, or other conventional VTE risk factors. Rather than serving as automatic contraindications, these characteristics should inform individualized pre-infusion assessment and the intensity of peri-infusion monitoring. Decisions regarding thromboprophylaxis should follow individualized assessment of thrombotic and bleeding risk; routine pharmacological thromboprophylaxis solely because a patient receives IV MSC therapy is not currently supported by sufficient evidence.

Interaction between patient and product risk

Patient- and product-related determinants are unlikely to operate independently. The clinical significance of MSC-associated coagulation activation may depend on the interaction between the procoagulant characteristics of the administered product, recipient susceptibility, and the magnitude of cellular exposure.

This relationship may be particularly complex in autologous therapy, where the underlying disease can potentially influence both recipient risk and cellular phenotype. Acosta et al. [16] reported peripheral microthrombotic events in patients with type 2 diabetes receiving autologous adipose-derived cell therapy and subsequently demonstrated reduced fibrinolytic activity in adipose-derived MSCs from diabetic patients. Although these findings do not establish diabetes as a contraindication, they provide proof-of-concept that patient disease may influence the hemostatic properties of an autologous cell product.

No validated algorithm currently integrates patient VTE risk with TF/CD142 expression, functional hemocompatibility, cell dose, concentration, or administration characteristics to quantitatively predict MSC-associated thrombosis [12]. Risk should therefore not be framed simply by classifying an MSC product as “thrombogenic” or “non-thrombogenic.” A more clinically relevant approach is to consider whether the biological and administration-related coagulation burden of a particular product is acceptable for a particular recipient.

Accordingly, thrombotic risk may be conceptualized through three interacting domains:

Patient susceptibility: previous VTE or thrombosis, hypercoagulability, systemic inflammation, malignancy, immobility, age, and relevant comorbidities.

Product thrombogenicity: TF/CD142 expression, PS exposure, functional coagulation activity, platelet interactions, viability, aggregation, dose/concentration, and post-thaw quality.

Administration exposure: formulation and suspension conditions, infusion volume and rate, repeated dosing, concomitant therapies, and peri-infusion management.

This patient-product-administration framework provides the clinical rationale for the risk-mitigation strategies discussed in Section 6.

Prevention and risk-mitigation strategies

Given the multifactorial nature of MSC-associated thrombogenicity, prevention should not rely on a single laboratory marker or intervention. Risk mitigation should integrate patient assessment, characterization of the final cell product, functional hemocompatibility testing, optimization of dose and administration conditions, and appropriate peri-infusion monitoring. Recent recommendations similarly emphasize standardized cell handling, careful administration, clinical monitoring, and preparedness for potential complications [19]. A proposed risk-mitigation framework is summarized in Table 3.

Patient selection and pre-infusion risk assessment

Baseline thrombotic risk should be assessed before IV MSC administration, with particular attention to previous VTE, active or recent thrombosis, systemic inflammation, malignancy, prolonged immobility, cardiovascular disease, and pre-existing coagulation abnormalities [15,19]. These conditions do not necessarily constitute absolute contraindications but may increase susceptibility to additional coagulation activation induced by an infused cellular product.

Pre-infusion evaluation should be individualized according to the patient's underlying disease and clinical condition. Platelet count and conventional coagulation parameters, with additional testing such as fibrinogen or D-dimer when clinically appropriate, may assist baseline assessment. However, no MSC-specific laboratory panel or validated clinical scoring system currently predicts thrombotic

Table 3: Proposed Risk-Mitigation Framework for Intravenous MSC Administration.

Domain	Risk factor / consideration	Proposed assessment or mitigation strategy	Current evidence and limitations	Key refs.
Patient	Previous VTE, active/recent thrombosis, thrombophilia, or coagulation abnormalities	Review thrombotic history and current clinical status before infusion; consider baseline platelet count and coagulation assessment according to individual risk	Conventional thrombotic risk factors are relevant, but no MSC-specific VTE prediction model or validated laboratory threshold is currently available	[19,46]
Patient	Systemic inflammation or hypercoagulable state	Assess severity of active inflammation and underlying disease; consider whether treatment timing may increase thrombotic vulnerability	Specific inflammatory or coagulation biomarker thresholds for withholding IV MSC therapy have not been established	[15,24,46]
Patient	Malignancy, immobility, advanced age, cardiovascular disease, and other conventional VTE risk factors	Incorporate conventional VTE risk factors into individualized benefit–risk assessment and peri-infusion monitoring	Clinical relevance is well established generally, but MSC-specific exclusion criteria are lacking	[19,46]
Product	TF/CD142 expression and activity	Characterize TF/CD142 in the final clinical product intended for intravascular administration	TF is mechanistically linked to MSC procoagulant activity, but no universally validated TF threshold predicts clinical thrombosis	[8,12,20-24]
Product	PS exposure, membrane integrity, and post-thaw quality	Evaluate viability together with membrane integrity and, when appropriate, PS exposure under clinically relevant post-thaw conditions	These parameters may influence procoagulant activity, but standardized clinical release thresholds are not established	[25,26,35]
Product	Functional interaction of the final product with blood	Consider TF activity, FXa/thrombin generation, plasma- or whole-blood coagulation assays, and platelet interactions as complementary assessments	Technical frameworks are emerging, but assay conditions and clinically predictive release thresholds remain incompletely standardized	[9,12,24,47]
Product	Reduced viability, cellular debris, or aggregation	Confirm adequate viability, suspension quality, and absence of clinically relevant aggregates immediately before administration	Conventional viability alone may not fully reflect hemocompatibility; universally accepted aggregate specifications are lacking	[5,29,31,35]
Administration	High total cell dose	Establish a product-specific, clinically justified dose considering product thrombogenicity and patient risk	Experimental and human studies suggest dose-dependent coagulation responses, but a universal safe MSC dose has not been established	[7,21,34,37,38]
Administration	High cell concentration or unfavorable suspension conditions	Optimize cell concentration, infusion volume, formulation, and suspension homogeneity; minimize conditions favoring aggregation	Total dose and concentration may have distinct effects, but standardized concentration limits across MSC products are unavailable	[19,24,36]
Administration	Infusion conditions and local cellular exposure	Use standardized product-specific administration procedures; maintain suspension homogeneity and avoid unintended rapid or high local cellular exposure unless supported by product-specific data	Comparative clinical evidence defining an optimal universal infusion rate is limited	[5,19]
Administration	Repeated IV exposure	Reassess patient status and product quality before subsequent administrations, particularly when cumulative cellular exposure is high	Clinical thrombotic events have been reported after repeated administration, but the independent contribution of cumulative exposure remains uncertain	[17]
Peri-infusion management	Consideration of anticoagulation in patients or products with elevated thrombotic risk	Consider anticoagulation only after individualized assessment of thrombotic and bleeding risks and within an appropriate clinical protocol	Heparin/LMWH and other approaches reduce MSC-associated coagulation experimentally, but routine prophylactic anticoagulation for all IV MSC recipients is not established	[11,34,39,48,49]
Peri-infusion management	Early coagulation activation or infusion-related complications	Monitor clinical status during and after infusion; consider D-dimer, fibrinogen, TAT, or other coagulation markers in higher-risk settings or prospective studies	Biomarker changes may indicate biological coagulation activation but should not be interpreted as equivalent to clinical thrombosis	[19]
Peri-infusion management	Suspected VTE or pulmonary complication	Promptly evaluate new dyspnea, chest pain, hypoxemia, limb pain/swelling, or other symptoms suggestive of thromboembolism according to standard clinical practice	Routine imaging of asymptomatic recipients is not supported by current evidence; evaluation should be clinically driven	[17-19,46]

Abbreviations: FXa: Activated Factor X; IV: Intravenous; LMWH: Low-Molecular-Weight Heparin; MSC: Mesenchymal Stromal Cell; PS: Phosphatidylserine; TAT: Thrombin–Antithrombin; TF: Tissue Factor; VTE: Venous Thromboembolism.

complications.

Patient risk should be interpreted together with product characteristics. In particular, administration of a product with substantial procoagulant activity may warrant greater caution in a recipient with baseline hypercoagulability. Thus, patient assessment and product characterization should be considered complementary components of risk management.

Product characterization and TF/CD142 assessment

Conventional MSC characterization typically includes identity, viability, sterility, purity, and potency-related parameters. For products intended for intravascular administration, these criteria may not adequately characterize interactions with circulating blood, supporting additional assessment of hemocompatibility [12].

TF/CD142 is an important candidate safety attribute because of its central role in initiating extrinsic coagulation. Experimental

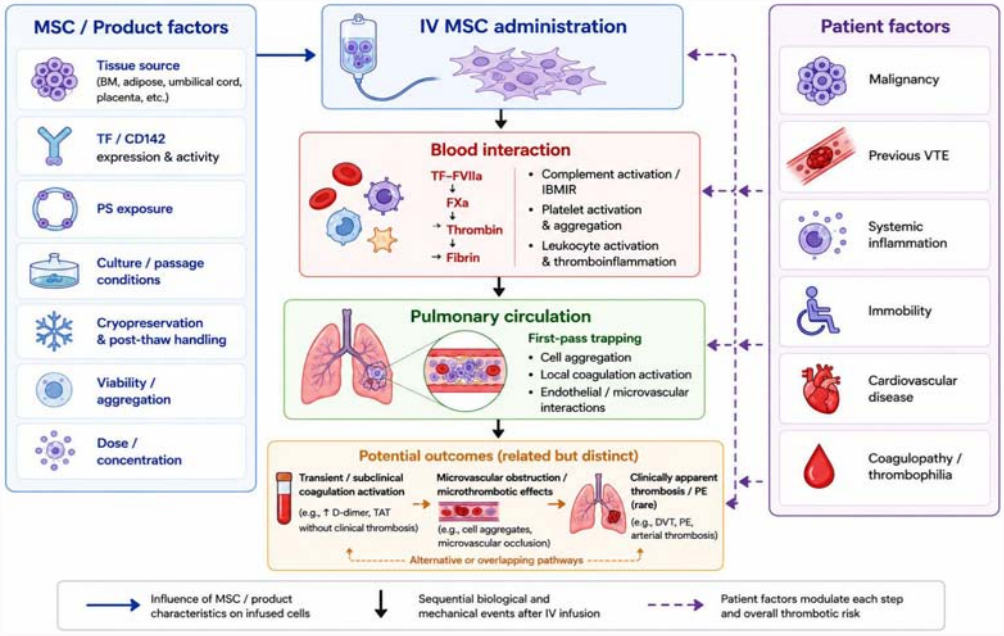

Figure 1: Proposed mechanisms and determinants of thrombotic risk following intravenous MSC administration.
Intravenously administered Mesenchymal Stromal Cells (MSCs) interact with circulating blood through multiple mechanisms, including Tissue Factor (TF/CD142)-mediated coagulation, Phosphatidylserine (PS) exposure, complement activation, Instant Blood-Mediated Inflammatory Reaction (IBMIR), and platelet and leukocyte interactions. MSC and product characteristics, including tissue source, manufacturing conditions, cryopreservation, viability, aggregation, dose, and concentration, influence these responses. Following IV administration, MSCs undergo pulmonary first-pass retention, which may be enhanced by cell aggregation and may interact with local coagulation activation. These biological and mechanical processes may result in transient or subclinical coagulation activation, microvascular obstruction, or, rarely, clinically apparent thrombosis or pulmonary embolism. Patient-related factors, including previous venous thromboembolism, malignancy, systemic inflammation, immobility, cardiovascular disease, and coagulopathy, may further modify the overall thrombotic risk. Importantly, pulmonary cell trapping, subclinical coagulation activation, and clinically manifest thrombosis represent related but distinct phenomena and should not be interpreted as equivalent outcomes.

studies demonstrate substantial product-dependent differences in TF expression and procoagulant activity, and reduction or elimination of TF can improve hemocompatibility and reduce coagulation responses [9,11,21-23].

Nevertheless, no universally validated TF/CD142 threshold predicts clinical thrombosis. Clinical observations have also shown that TF expression does not necessarily correlate with post-infusion coagulation biomarkers [24]. TF/CD142 should therefore be regarded as an important mechanistic and product-related risk attribute, but not as an isolated binary release criterion.

Functional hemocompatibility testing

Phenotypic TF/CD142 measurement does not capture the overall functional interaction between an MSC product and circulating blood. Functional assays may therefore complement conventional product characterization [12,21,47].

Potential approaches include TF activity, FXa generation, thrombin generation, plasma-based coagulation assays, and whole-blood hemocompatibility testing. Thrombin generation assays may be particularly useful because they integrate multiple pro- and anticoagulant influences. For example, calibrated automated thrombography has been used to quantify thrombin generation in clinical-grade MSC products derived from bone marrow, adipose tissue, and umbilical cord tissue and to assess the effects of anticoagulation on their procoagulant activity [48].

Emerging technical frameworks support standardized assessment of MSC-blood compatibility [12,47]. However, assay results depend on cell concentration, blood or plasma source, reagents, preanalytical conditions, and analytical platforms. Clinically validated universal release thresholds for TF activity, FXa generation, thrombin generation, or other functional assays have not yet been established. Functional hemocompatibility testing should therefore currently be viewed as an evolving component of product-specific safety characterization.

Optimization of cell dose, concentration, and suspension quality

MSC-associated coagulation responses can be dose dependent [7,21,34,37,38]. Experimental studies demonstrate increasing coagulation activity with increasing cellular exposure, and dose-dependent coagulation and fibrinolytic activation has also been observed in humans without clinically apparent thromboembolism [38].

These findings support dose as an important modifier of MSC-blood interactions but do not establish a universal maximum IV MSC dose. The relationship between dose and thrombogenicity depends on tissue source, TF phenotype, manufacturing, recipient characteristics, and administration conditions.

Cell concentration should also be distinguished from total dose. Highly concentrated suspensions may promote cell–cell interactions and aggregation, while formulation and post-thaw conditions can influence recovery and stability [36]. Because aggregates may further increase pulmonary microvascular obstruction, dose, concentration, formulation, and suspension quality should be validated together for

the specific clinical product.

Anticoagulation and thromboprophylaxis

Experimental and translational studies demonstrate that anticoagulant approaches can attenuate MSC-associated coagulation responses. Heparin and LMWH have reduced coagulation abnormalities, thrombin generation, and pulmonary thrombotic effects in experimental systems, while other anticoagulant strategies have also been investigated [11,34,39,48,49].

These findings provide a biological rationale for anticoagulation but do not establish routine prophylactic anticoagulation as a universal requirement for IV MSC therapy. Anticoagulants carry bleeding risk, and the optimal agent, dose, timing, duration, and target population have not been established specifically for MSC administration. Furthermore, anticoagulation should not substitute for appropriate product characterization.

Decisions regarding thromboprophylaxis should therefore be individualized according to patient thrombotic and bleeding risks and established clinical indications, while MSC-specific prophylactic strategies require further prospective evaluation.

Cryopreservation, post-thaw handling, and infusion preparation

For cryopreserved MSC products, product quality may change between thawing and administration. Freeze-thawing can alter membrane integrity, cellular function, and blood interactions, while post-thaw formulation and storage influence cell recovery and stability [30,35,36].

Post-thaw procedures should therefore be standardized for each product, including thawing, washing or dilution, reconstitution, final cell concentration, holding time, mixing, and control of aggregation. Importantly, a high viability percentage alone does not establish adequate hemocompatibility. Viability should be considered together with recovery, membrane integrity, suspension stability, aggregation, and, where appropriate, functional hemocompatibility testing [12,47].

Infusion procedure and peri-infusion monitoring

Administration procedures should be standardized because IV MSCs initially encounter the pulmonary circulation and undergo substantial first-pass retention [5]. Relevant parameters include cell concentration, infusion volume and rate, line management, and administration duration, although no single optimal infusion protocol is applicable to all MSC products [19].

During infusion, patients should be monitored for acute respiratory or cardiovascular abnormalities, including dyspnea, hypoxemia, chest pain, tachycardia, and hypotension. Post-infusion observation should reflect the product, administered dose, patient condition, and institutional protocol. Routine imaging for pulmonary embolism in asymptomatic recipients is not currently supported; diagnostic imaging should be performed when clinically indicated.

Toward an integrated risk-based approach

No single intervention can eliminate the potential thrombotic risk associated with IV MSC administration. Current evidence instead supports integration of patient susceptibility, product thrombogenicity, and administration exposure. Table 3 summarizes the major variables and proposed mitigation strategies across these domains.

Importantly, this framework remains conceptual rather than quantitatively validated. MSC-specific TF/CD142 thresholds, functional hemocompatibility release criteria linked to clinical outcomes, universal dose limits, and standardized anticoagulation protocols remain to be established [12,47].

Prospective studies linking standardized product characteristics and administration variables with serial coagulation biomarkers and adjudicated thrombotic outcomes will be required to determine which combinations of factors most reliably predict clinically meaningful risk.

Discussion and Future Perspectives

Intravenous administration remains one of the most practical routes for systemic MSC therapy, but direct exposure of living cells to circulating blood creates safety considerations that differ fundamentally from those of conventional soluble therapeutics. Experimental studies have established that MSCs can express TF/CD142, expose procoagulant phospholipid surfaces, activate coagulation and complement pathways, interact with platelets and innate immune cells, and undergo early retention within the pulmonary microcirculation [5-14,21,25,27-31,33,34]. These findings provide a clear biological basis for concern regarding coagulation activation and thrombotic or microembolic complications.

Nevertheless, the clinical significance of these biological properties remains incompletely defined. Clinically significant thrombotic events have been reported in individual patients, and controlled human studies have demonstrated transient or dose-dependent activation of coagulation and fibrinolysis without overt thrombosis [16-18,24,38]. In contrast, randomized trials and systematic reviews have not identified thrombotic or thromboembolic events as a consistent safety signal following intravascular MSC administration [3,4,40]. These observations are not necessarily contradictory. Rather, they indicate that procoagulant potential, subclinical coagulation activation, and clinically manifest thrombosis represent related but distinct outcomes.

Interpreting procoagulant potential in the context of clinical risk

TF/CD142 is among the most consistently identified determinants of MSC-associated coagulation. Differences in TF expression are associated with differences in functional procoagulant activity, and experimental reduction or elimination of TF can improve hemocompatibility [8,21-23]. However, TF expression varies according to tissue source, donor, culture conditions, and manufacturing processes, and a direct relationship between TF levels and clinical thrombosis has not been established [6,21,24].

TF/CD142 should therefore be regarded as an important risk-associated product attribute rather than a stand-alone clinical predictor [12,20,24]. The same principle applies to functional measurements such as TF activity, FXa generation, and thrombin generation. These assays can characterize the interaction of an MSC product with the coagulation system, but clinically validated thresholds capable of predicting thrombotic events are currently lacking [12,21,47,48]. Consequently, neither TF expression nor an isolated functional coagulation assay should presently be interpreted as a universal binary release criterion.

This distinction may help reconcile the apparent discrepancy between experimental and clinical evidence. A product may possess measurable procoagulant activity without causing clinically significant

thrombosis when administered under controlled conditions, whereas the clinical consequences of the same biological activity may differ according to cellular exposure, recipient susceptibility, and administration procedures.

Product-specific hemocompatibility and pulmonary interactions

Tissue origin provides useful biological context but is insufficient to predict intravascular safety because substantial variability exists both between and within MSC sources [6,9,11,21,24]. Manufacturing, cryopreservation, post-thaw handling, formulation, and other product-specific variables can further modify hemocompatibility. Accordingly, safety assessment should increasingly focus on the final manufactured and formulated MSC product, integrating phenotypic and functional parameters rather than relying on tissue source or TF/CD142 alone [12,21,25,47]. Emerging technical frameworks support this route-specific approach, although assay standardization and clinically validated thresholds remain important unmet needs.

Pulmonary retention should also be interpreted within this product-specific framework. IV-administered MSCs commonly undergo early pulmonary trapping because of their size and adhesive properties [5,31-33]. This phenomenon should not itself be equated with pulmonary thromboembolism. Pulmonary cell trapping reflects biodistribution and mechanical retention, whereas thromboembolism involves pathological vascular obstruction associated with thrombotic processes. Nevertheless, the two mechanisms may interact: high cell concentrations, aggregates, or enhanced adhesion may increase microvascular obstruction, while TF- and PS-mediated coagulation around retained cells may promote localized thrombin and fibrin formation [8,14,21,25,34]. Future studies should therefore clearly distinguish pulmonary cell retention, mechanical microvascular obstruction, coagulation activation, microthrombosis, and clinically diagnosed pulmonary embolism.

Toward an integrated patient–product–administration risk model

The available evidence supports an integrated framework in which thrombotic risk emerges from interactions among patient susceptibility, product thrombogenicity, and administration exposure. Rather than assigning risk to a single biomarker, cell source, dose, or patient characteristic, this framework emphasizes the convergence of biological and clinical determinants. However, it remains conceptual rather than quantitatively validated, and no MSC-specific algorithm currently assigns validated weights to these variables or reliably predicts clinical thrombosis.

This framework also provides an appropriate context for considering anticoagulation. Experimental and translational studies demonstrate that heparin, LMWH, and other anticoagulant approaches can attenuate MSC-associated coagulation responses [11,34,39,48,49]. However, these findings do not establish routine prophylactic anticoagulation as a universal requirement for IV MSC therapy. Anticoagulation carries bleeding risk, and optimal patient selection, agent, dose, and timing have not been established specifically for MSC administration. Its use should therefore remain individualized according to patient thrombotic and bleeding risks and should not substitute for appropriate product characterization.

Future research priorities

Future studies should focus on several areas required to translate mechanistic understanding into clinically useful safety criteria. First, TF/CD142 measurements and functional hemocompatibility assays should be standardized and evaluated prospectively against clinically adjudicated thrombotic outcomes. Second, studies should systematically report product and administration variables, including total cell dose, concentration, formulation, post-thaw handling, and infusion conditions, consistent with recent consensus recommendations emphasizing standardized reporting of MSC product characteristics and administration parameters [50]. Third, coagulation biomarkers should be assessed at predefined time points to clarify the relationship between transient biological activation and clinically meaningful events. Fourth, standardized terminology should distinguish pulmonary cell trapping and mechanical obstruction from microthrombosis and clinically diagnosed thromboembolism. Finally, prospective studies should determine whether multivariable approaches integrating patient susceptibility, product hemocompatibility, and administration exposure provide greater predictive value than individual biomarkers such as TF/CD142 alone.

These efforts should be directed toward refining the safety of systemic MSC therapy rather than implying that IV administration is intrinsically unsafe. The accumulated randomized clinical evidence remains generally reassuring [4,40]. The principal unresolved question is therefore not whether MSCs can exhibit procoagulant activity, but under what combination of patient, product, and administration conditions that biological activity becomes clinically relevant. Addressing this question will be essential for developing evidence-based safety criteria for systemic MSC therapy.

Conclusion

Intravenous MSC administration has a generally favorable clinical safety profile, but direct contact between MSCs and circulating blood introduces a biologically plausible risk of coagulation activation and thromboembolic complications. TF/CD142-mediated coagulation, PS exposure, platelet interactions, IBMIR, and pulmonary microvascular trapping represent interconnected mechanisms that may contribute to this risk. The magnitude of these responses may vary according to MSC tissue source, donor characteristics, manufacturing conditions, cryopreservation and post-thaw handling, cell dose and concentration, suspension quality, and administration conditions.

Clinically significant thrombotic complications have been reported following IV MSC administration, while transient or subclinical coagulation activation may occur in the absence of clinically apparent thrombosis [17,18,24,38]. However, systematic reviews and meta-analyses have not demonstrated a consistent increase in clinically significant thrombotic or thromboembolic events following intravascular MSC administration under controlled clinical conditions [3,4,40]. Thus, procoagulant potential, subclinical coagulation activation, and clinically manifest thrombosis should be regarded as related but distinct outcomes, and experimentally measurable procoagulant activity should not be considered equivalent to clinical thrombosis.

Current evidence supports a patient–product–administration risk-based approach to IV MSC therapy. TF/CD142 is an important mechanistic and product-related risk attribute, but no single biomarker currently provides sufficient predictive value to determine clinical thrombotic risk. Integrating patient-specific thrombotic risk assessment, product characterization, functional hemocompatibility testing, product-specific dose and administration procedures, and

appropriate peri-infusion monitoring may provide a more rational strategy for improving safety. Future prospective studies linking standardized product-level coagulation and hemocompatibility assays with well-defined clinical thrombotic outcomes will be essential to establish clinically validated risk thresholds and evidence-based prevention strategies for systemic MSC therapy.

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