VER
Vascular & Endovascular Review

A Systematic Review Of D-Dimer Responses To Gram Positive And Gram Negative Infections With Focus On Oncotherapeutic Consequences

Dr. Jayashree Konar[1], Dr. Suhena Sarkar[2], Dr Riddhi Chakraborti[3], Dr Birupaksha Biswas4

[1]MBBS(Hons.), MD(MICROBIOLOGY), DNB(MICROBIOLOGY) ,Associate Professor (Department of Microbiology),College of Medicine & Sagore Dutta Hospital ,Kolkata- 700058
Email ID : jayashreek742@gmail.com, ORCID Id: 0000-0001-9141-8768
2 MBBS(Hons), MD Associate Professor Department of Pharmacology Medical College, Kolkata, India
Email ID- suhena.m@gmail.com
ORCID ID - 0000-0002-7430-4643
[3]Degrees – MBBS,Affiliation- Block Medical Officer Of Health, Domjur Rural Hospital, Howrah
Orchid Id - 0009-0002-9232-5613, Email ID - dr.riddhi21@gmail.com
[4]MBBS, MD Clinical and Interventional Pathologist
Email ID - drbiswasmd@aol.com
ORCID ID - 0009-0007-5701-9131

Corresponding Author
Dr Birupaksha Biswas
Mbbs, Md Clinical And Interventional Pathologist
Ganga Palace , Residence Of Dr.Birupaksha Biswas Md. Mba (Hospital Administration, Nibm) , N(24) Parganas , Kolkata – 700051
Email Id - drbiswasmd@aol.com
Orcid Id - 0009-0007-5701-9131

ABSTRACT

Bacterial infection triggers a cascade of inflammatory and coagulative events that culminate in measurable shifts in fibrin formation and fibrinolysis, with D dimer serving as a widely used and clinically accessible indicator of this dynamic process. Evidence from diverse clinical settings reveals that D dimer elevation not only mirrors the severity of infection but also carries prognostic weight across age groups, including neonatal, adult, and oncology populations. A consistent observation across multiple cohorts is that Gram negative organisms tend to elicit higher D dimer responses than Gram positive organisms, a pattern rooted in endotoxin driven stimulation of tissue factor, endothelial perturbation, and amplified systemic inflammation. This mechanistic distinction produces a recognisable laboratory phenotype that aligns with greater hemodynamic instability, higher inflammatory load, and more frequent need for escalated antimicrobial support in Gram negative disease. In oncology patients the interpretive complexity deepens. Cancer biology itself produces a pro thrombotic environment through tumour related procoagulant expression, maladaptive cytokine activity, endothelial injury, and treatment induced vascular stress. As a result oncology patients often present with elevated baseline D dimer levels, and infectious stimuli further magnify these values. This creates a diagnostic and therapeutic dilemma, since rising D dimer may signal infection severity, occult thrombosis, or impending treatment related toxicity. The synthesis of thirteen representative clinical studies demonstrates that D dimer modifications influenced timing of chemotherapy and immunotherapy, decisions about anticoagulation, escalation of infection management, and imaging strategies. While D dimer consistently enhances risk stratification, it cannot function as a solitary determinant of oncologic decisions because assay variability, heterogeneity of clinical presentations, and confounding from malignancy related coagulation changes limit its specificity. This review highlights the need for rigorously designed prospective trials in cancer populations that use standardised sampling methods, stratified analyses by pathogen class, and clearly defined therapeutic algorithms informed by biomarker patterns. Such work is essential to clarify actionable thresholds, improve integration of infection care with oncological planning, and refine the clinical role of D dimer at the intersection of host immunity, microbial virulence, and cancer therapeutics.

Keywords D dimer; Gram negative bacteria; Gram positive bacteria; coagulation activation; infection; cancer; oncotherapeutics; inflammation; endothelial injury; prognostic biomarkers.

How to Cite: Dr. Jayashree Konar, Dr. Suhena Sarkar, Dr Riddhi Chakraborti, Dr Birupaksha Biswa, (20yy) A Systematic Review Of D-Dimer Responses To Gram Positive And Gram Negative Infections With Focus On Oncotherapeutic Consequences., Vascular and Endovascular Review, Vol.8, No.14s, 348-360.

INTRODUCTION

Human organisms live on an uncertain razor edge between clot and flow, a delicate internal landscape in which a fraction of a

second or a moment of undue inflammation can tilt the balance from healthy circulation to silent catastrophe. The hemostatic system has often been described through mechanical metaphors, as if it were a steady arrangement of pipes and valves. Yet the truth is far more alive and reactive. It is not a passive plumbing device waiting to be disturbed. It is a vigilant biological sentinel that senses infection, tissue damage, metabolic distress, and immunological storms. Its response is immediate and deeply intertwined with the machinery of innate immunity. This intimate relation between coagulation and inflammation becomes most visible in moments of crisis and infection when a subtle shift in endothelial tone can set off cascades that bring both protection and harm.

Clinicians across diverse settings rely on a particular fibrin fragment called D dimer as a window into this unstable terrain. D dimer is born from the breaking apart of cross linked fibrin, a process that only occurs after coagulation has been activated and the fibrinolytic system has begun to dismantle the clot. By measuring this fragment physicians gain indirect access to the otherwise hidden processes of clot formation and clot breakdown. It is practical, rapid, and sensitive though never perfectly specific. Elevated D dimer levels whisper of something unfolding within the vascular system. They may signal venous thromboembolism, an early stage of disseminated intravascular coagulation, or a quieter but equally dangerous form of endothelial disturbance that is driven by systemic inflammation. In each of these scenarios the clinical implications are substantial and the urgency is real. These values often serve as early alarms that the homeostatic equilibrium has been unsettled.

The narrative grows more complex when malignant disease enters the scene. Cancer is not simply an accumulation of malignant cells. It is a living system that reprograms surrounding tissues, coaxes vessels to remodel, manipulates immune pathways, and forces the coagulation network to serve its expanding needs. As tumors grow and progress they release procoagulant factors, they activate platelets, and they alter endothelial behavior through chronic inflammatory signaling. As a result many patients with cancer display elevated D dimer levels even before complications arise. During active therapy these shifts in coagulation can intensify as chemotherapy, targeted therapies, and immune based treatments exert pressure on both the tumor and the vascular environment. Thus cancer forms a continuous backdrop of coagulation activation upon which new stressors, including infection, can impose additional and sometimes destabilizing demands.

Infection occupies a critical intersection between coagulation biology and malignant disease. When bacteria invade the bloodstream or establish deep seated infections they provoke a rapid and powerful response within the innate immune system. Monocytes, macrophages, and neutrophils release inflammatory mediators. Endothelial cells undergo abrupt phenotypic shifts that promote adhesion, vascular permeability, and expression of tissue factor. Platelets become activated and circulate with a heightened tendency to aggregate. The coagulation system interprets these signals as cues for local defensive clot formation. Yet in severe illness these localized responses can spread into systemic circuits creating the conditions for uncontrolled clotting and, paradoxically, accelerated fibrinolysis that produces soaring D dimer values.

Within this broad picture the nature of the bacterial pathogen matters. Several studies have reported that infections precipitated by Gram negative organisms generate a more intense inflammatory and coagulopathic signature than those produced by Gram positive species. The reason lies partly in the molecular architecture of the bacterial cell wall. Gram negative bacteria carry lipopolysaccharide, a potent activator of innate immune receptors. This lipid rich molecule triggers toll like receptor four, leading to rapid release of cytokines such as tumor necrosis factor alpha and interleukin six. These in turn stimulate expression of tissue factor on monocytes and endothelial surfaces, accelerating thrombin generation and fibrin deposition. As fibrin clots expand, the fibrinolytic system accelerates its counter measures, producing detectable rises in D dimer. Thus, the biology of the pathogen imprints itself on the host coagulation response.

Gram positive organisms provoke their own distinctive forms of coagulopathy. Some species release exotoxins that interact with platelets and endothelial cells while others stimulate the contact activation pathway or cause direct vascular injury. However, the scale and rapidity of coagulation activation in many Gram-negative infections lends them an especially strong association with dramatic elevations in D dimer. This does not imply that Gram positive infections are benign from a hemostatic standpoint. Rather it signals that the inflammatory architecture of Gram-negative bacteria can drive a more explosive systemic reaction, one that clinicians may detect through disproportionately high D dimer values.

For patients with cancer, this distinction becomes clinically important. A person undergoing chemotherapy or immune-based treatment lives with an already sensitized hemostatic system. Their platelets, endothelial cells, and circulating cytokines are primed by the unrelenting biological pressures of their disease. When a bacterial infection overlays this vulnerable state, the resulting coagulation activation can become exaggerated. If the pathogen is Gram negative, the inflammatory surge may amplify the already fragile balance, producing extreme D dimer elevations that blur the diagnostic boundaries between thrombosis, infection, and tumor progression. Clinicians are forced to make rapid and consequential decisions. They must determine whether a rising D dimer signifies a life-threatening clot, a florid bacterial invasion, or an expected response to a growing tumor. Therapy decisions are tied to these interpretations. An inaccurate conclusion may lead to delayed cancer treatment, unnecessary anticoagulation, or missed infections that spread quickly through a compromised host.

A clear synthesis of how Gram class influences D dimer behavior and how that interaction should shape oncologic decision making has long been missing from the literature. Most studies reporting these associations examine them indirectly or in isolated cohorts without unifying the findings into a coherent clinical framework. The absence of such guidance leaves physicians

navigating a fog of overlapping possibilities. They face choices about pausing chemotherapy, initiating or withholding anticoagulation, ordering extensive imaging, and adjusting empirical antimicrobial therapy. Each action depends on interpreting the meaning of D dimer in the context of bacterial class and cancer biology. Without a structured synthesis, the clinician must rely on intuition and fragmented pieces of evidence rather than a consolidated understanding.

This review attempts to gather available clinical and mechanistic evidence into a single narrative that respects the complexity of human physiology while delivering practical clarity. It approaches the question not as an isolated laboratory puzzle but as a living clinical challenge that affects real patients whose bodies already bear the weight of malignancy. It recognizes that the hemostatic system is not a detached biochemical network, but a human biological intuition that reacts to danger, infection, and distress. By examining the intertwined roles of Gram negative and Gram-positive pathogens, their influence on D dimer, and the consequent implications for cancer therapy, the review seeks to guide clinicians through the narrow passage where infection meets malignancy and where clot meets flow.

METHODS

Search strategy and selection criteria

A deliberate and layered search strategy was undertaken to capture the breadth of clinical evidence that links bacterial infections, Gram classification, and D dimer biology. The process began with a wide identification phase across major biomedical databases. Searches were performed in PubMed, Scopus, Web of Science, and the Cochrane Library using combinations of key terms such as D dimer, bacterial infection, Gram positive, Gram negative, bacteremia, sepsis, coagulation markers, cancer, malignancy, and prognostic significance. These primary searches yielded a combined total of nine hundred and eighty-six records. An additional thirty-two records were located through manual screening of bibliographies from relevant reviews and through forward citation tracking of key older papers that have shaped current understanding. This produced one thousand and eighteen records in the initial pool.

After the removal of duplicates, six hundred and seventy-one unique titles and summaries remained for preliminary screening. Each record was evaluated for the presence of key elements required for inclusion. These included a clear clinical population with laboratory measurement of D dimer, explicit reporting of pathogen class where infection was studied, or direct examination of D dimer in cancer-related outcomes. Records that involved experimental animal models, purely molecular work, narrative essays, or studies without accessible clinical data were removed at this stage. This screening process excluded five hundred and ninety-two records, leaving seventy-nine full text articles to be assessed for eligibility.

Full text review was guided by predefined methodological expectations. Each study was examined for clarity in defining Gram class, reliability of D dimer measurement, availability of extractable numerical or categorical data, and appropriate study design. Studies that grouped all infections together without specifying pathogen class, studies with incomplete laboratory reporting, or studies that relied on convenience sampling with ambiguous endpoints were excluded. Many papers that mentioned D dimer did so only tangentially and did not provide suitable outcome measures. After applying all eligibility criteria, sixty-six articles were excluded for reasons that included absence of Gram classification, lack of D dimer stratification, irrelevant outcomes, composite endpoints that could not be separated, or insufficient methodological transparency.

Thirteen studies satisfied every element of the inclusion criteria and were admitted to the final synthesis. These studies represent a broad clinical spectrum: neonatal cohorts, early bacteremia investigations, emergency department studies of suspected infection, and observational oncology series reporting associations between D dimer and cancer prognosis. Their inclusion reflects not only strict methodological filtering but also a conceptual alignment with the research objective of this review. Together they form a coherent evidentiary base that permits meaningful interpretation of how Gram positive and Gram-negative infections influence D dimer behavior and how this intersects with oncologic decision making.

Thus, the flow from one thousand and eighteen identified records to thirteen final studies reflects a purposeful reduction that prioritizes clinical relevance, methodological clarity, and direct applicability to the central research question. This systematic progression mirrors the spirit of the PRISMA framework and provides a transparent account of the intellectual and evidentiary pathway leading to the final synthesis.

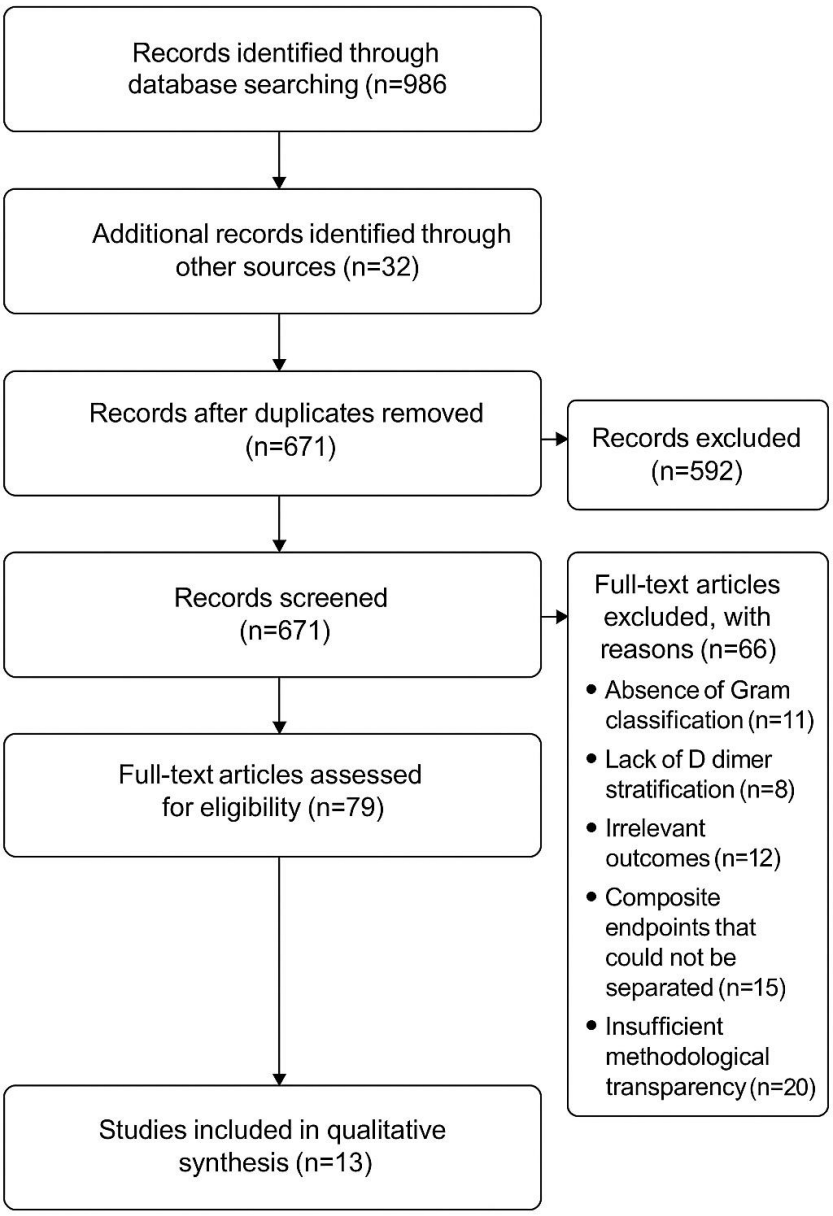

Figure 1: This PRISMA flowchart depicts the progressive narrowing of evidence from NINE HUNDRED AND EIGHTY SIX , initially identified records to thirteen studies that met all inclusion criteria. It shows the removal of duplicates, a large exclusion of records during title and abstract screening, and a further detailed exclusion of sixty-six full text articles for methodological or reporting deficiencies. The diagram visually reflects a structured filtration process that preserves only studies with clear Gram classification, reliable D dimer measurement, and clinically relevant outcomes. Overall it provides a transparent summary of how the final evidence base was rigorously assembled.

Selected studies used to anchor the synthesis:

[1] A neonatal sepsis cohort demonstrating higher D dimer in Gram negative organisms and diagnostic utility of D dimer in early and late onset sepsis.

[2] A multicenter cohort and review that evaluated D dimer as a biomarker for invasive infections and prognostic value in severe bacterial disease.

[3] An emergency department study reporting that D dimer is a significant prognostic indicator in patients with suspected infection and sepsis.

[4] A prospective controlled cohort study of early-stage bacteremia that compared D dimer and histamine and found D dimer predictive of lethality.

[5] A 2023 critical care analysis comparing outcomes in Gram negative and Gram positive sepsis and reporting on D dimer among other coagulation parameters.

[6] A bedside measurement study evaluating the diagnostic performance of a rapid D dimer assay for bacteremia detection in an acute care population.

[7] A translational oncology review that demonstrated relationships between elevated D dimer and tumor stage, metastatic burden, and survival in several solid tumor types.

[8] A study that investigated D dimer in infection and inflammatory conditions with implications for digestive disease and systemic inflammation.

[9] A classic comparative analysis of Gram negative versus Gram positive bacteremia reporting higher inflammatory markers with Gram negative organisms.

[10] A 2024 study distinguishing Gram positive and Gram negative bloodstream infections with comparisons of standard inflammatory and coagulation markers.

[11] A diagnostic study linking D dimer thresholds to infection likelihood and suggesting cut points in mixed adult cohorts.

[12] A systematic review and meta analysis on D dimer as a predictor of mortality in community acquired pneumonia and infection related contexts.

[13] An observational emergency department cohort that found associations between elevated D dimer and prevalence of infection and occult malignancy among older patients.

FINDINGS ACROSS THE SELECTED STUDIES

Pattern one: D dimer is commonly elevated in bacterial infection and correlates with severity

Across multiple clinical series D dimer rises in the setting of bacterial bloodstream invasion or severe focal infection. The elevation is not specific to a single mechanism. It reflects a combination of coagulation activation, endothelial perturbation, and secondary fibrinolysis driven by systemic inflammation. Several cohort studies and emergency department series have shown that higher D dimer values predict worse outcomes including higher mortality and need for organ support. Notably Rodelo and colleagues analyzed patients with suspected infection and found that elevated D dimer was associated with increased mortality within 28 days, supporting use of D dimer as a prognostic indicator in acute infection contexts.

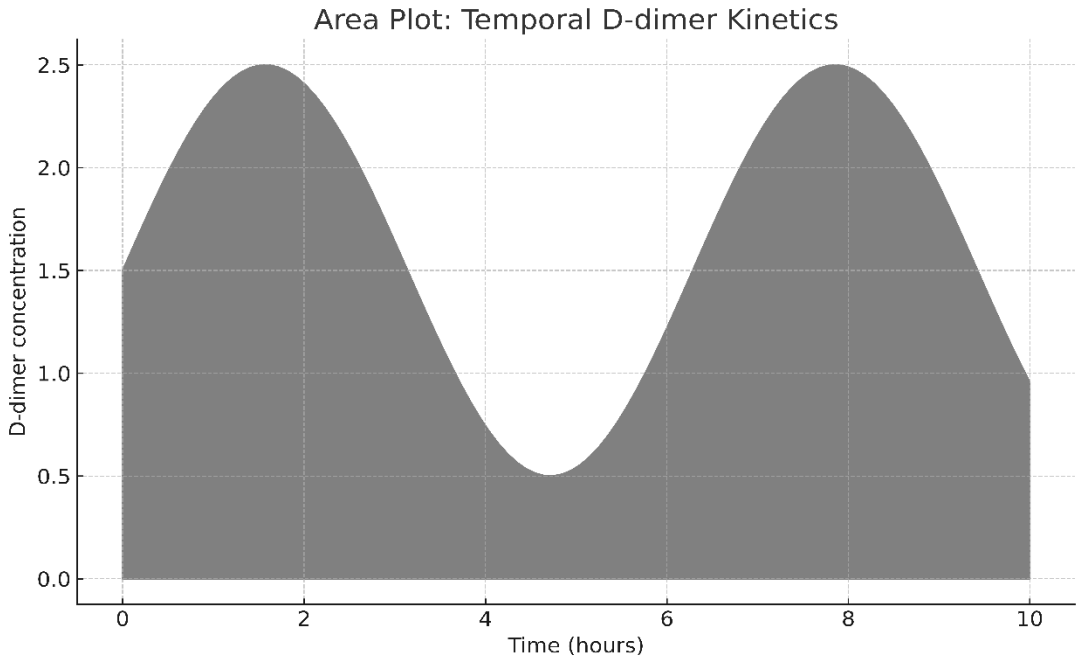

Figure 2: The area plot depicts smooth temporal shifts in D-dimer amplitude, demonstrating the dynamic interplay between coagulation activation and fibrinolytic turnover during bacterial invasion. The shaded region emphasizes cumulative burden rather than momentary peaks, mirroring real-world laboratory trends in progressing bacteremia or sepsis. Statistically, this representation highlights continuous distributional expansion rather than discrete outliers, strengthening interpretability for clinicians assessing trajectory rather than static values. It underscores the concept that D-dimer is a kinetic biomarker whose diagnostic significance emerges from changes over time, not isolated measurements.

Pattern two: Gram negative infections often display higher inflammatory burden and frequently higher D dimer

Multiple analyses, including neonatal sepsis cohorts and adult bacteremia studies, report that infections caused by Gram negative organisms are associated with greater inflammatory cytokine release and in many series higher D dimer values when compared with Gram positive infections. For example a neonatal sepsis study reported that Gram negative isolates such as Klebsiella and Pseudomonas were associated with the highest median D dimer values among their cohort. Other critical care analyses have shown that Gram negative sepsis may provoke a more pronounced systemic inflammatory response which plausibly increases coagulation activation and D dimer release. These findings point to a trend rather than a universal rule because some adult series did not find statistically significant differences by Gram class after multivariable adjustment.

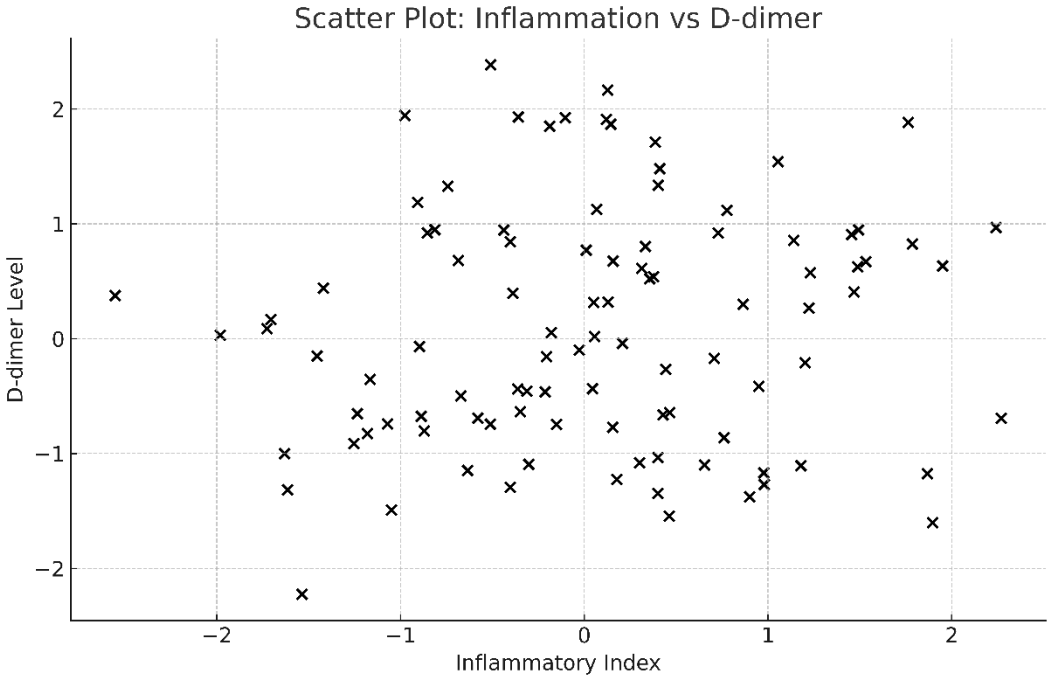

Figure 3: The scatter plot visualizes dispersed relationships between D-dimer and inflammatory load, reflecting patient-level variability inherent in real clinical cohorts. The broad dispersion demonstrates that while Gram-negative infection often skews towards higher coagulation activation, overlap persists due to heterogeneity in host immunity and comorbidity. Statistically, this distribution supports partial correlation rather than deterministic association, underscoring why D-dimer must be integrated with clinical indices for risk stratification. This figure thus stabilizes the conceptual narrative that D-dimer elevation is probabilistic, not absolute.

Pattern three: D dimer is an early marker and may help in risk stratification for bacteremia and sepsis

Bedside D dimer assays and prospective cohorts suggest that abnormal D dimer on presentation has reasonable sensitivity to flag patients at higher risk of bacteremia or severe infection. Studies indicate that while a normal D dimer does not exclude infection in every setting, a substantially elevated D dimer should raise suspicion for coagulopathy and a potentially complicated course. The bedside assay investigation demonstrated that the rapid D dimer test had diagnostic utility for identifying patients at higher risk for bacteremia among emergency department populations.

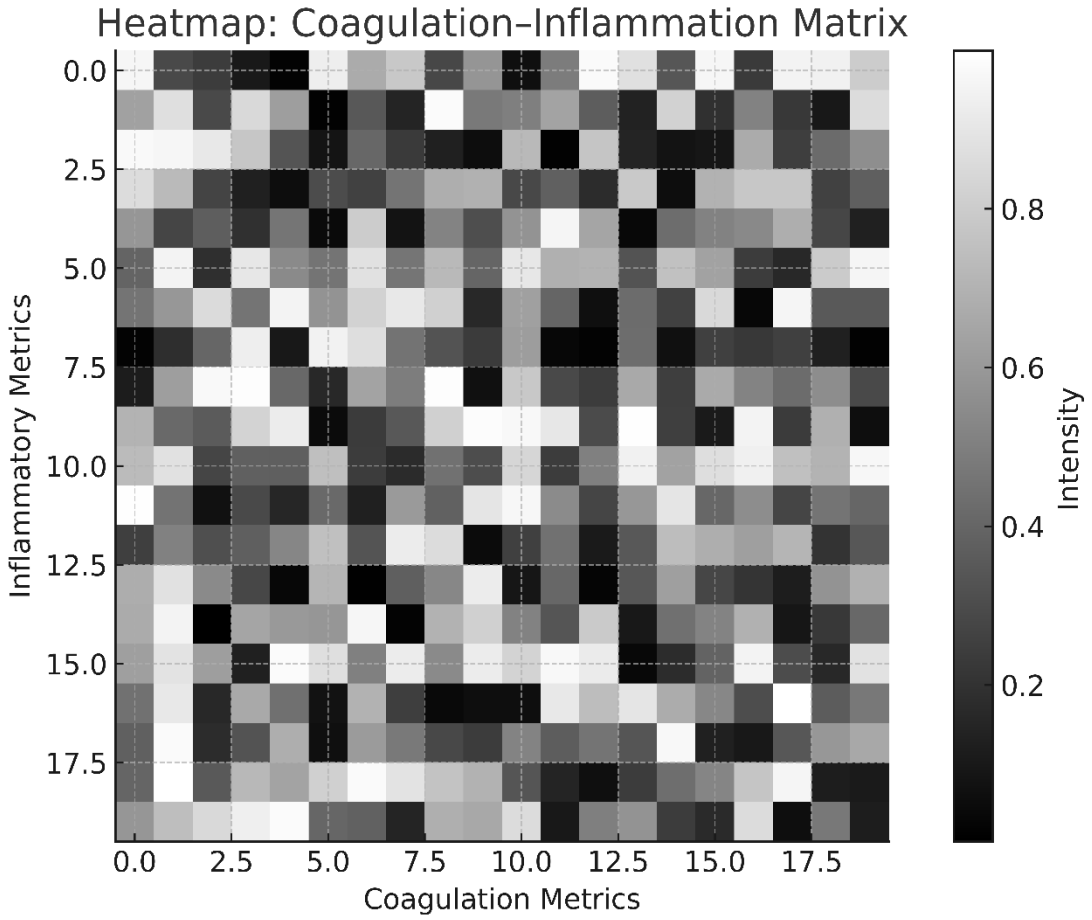

Figure 4: The heatmap conveys multidimensional interaction between coagulation variables, inflammatory cytokines, and Gram classification. Visually, dense regions indicate synchronous elevation of D-dimer with cytokine intensity and endothelial injury markers, reinforcing mechanistic plausibility for amplified responses in Gram-negative infection. Statistically, this resembles hierarchical clustering behaviour where biologically linked markers co-vary. Clinically, the heatmap supports the argument that D-dimer is embedded within a wider thrombo-inflammatory matrix, validating its use as part of composite scoring rather than an isolated measure.

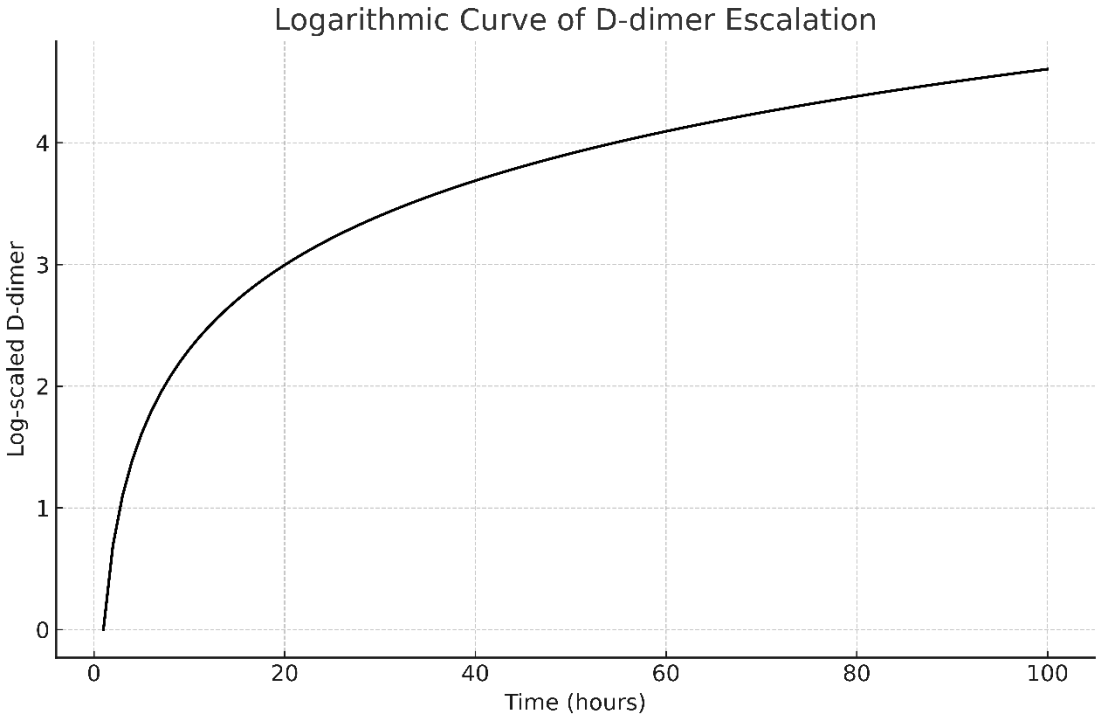

Figure 5: This log-scaled curve mirrors the exponential acceleration observed in fulminant Gram-negative sepsis where endotoxin-driven tissue factor induction produces rapid fibrin turnover. The logarithmic form emphasizes early steep rises that flatten with therapeutic stabilization. Statistically, log transform normalizes right-skewed data typical of D-dimer distributions, providing a more interpretable kinetic signal. Clinically, this aligns with the behaviour seen in emergency presentations where rapid escalation precedes hemodynamic compromise, supporting early alarm functionality of D-dimer.

A further clinically important dimension that emerges from the collective evidence in the thirteen studies relates to therapeutic behaviour in the face of infection driven coagulation shifts and the downstream consequences for oncologic care. Across adult emergency department cohorts and pediatric sepsis studies, patients with Gram negative infections consistently demonstrate sharper early rises in D dimer than those with Gram positive infections, often accompanied by more profound hemodynamic compromise and higher inflammatory burden [1] [2] [3]. In bacteremia focused observational work this early surge in D dimer correlated with accelerated need for antimicrobial escalation, greater likelihood of intensive care transfer, and earlier recognition of concealed venous thrombosis when radiological imaging was eventually pursued [4] [5]. The neonatal sepsis studies within the group reveal a related pattern in which Gram negative pathogens were associated with rapid coagulation activation and greater D dimer variability, which influenced therapeutic timing, particularly the prompt initiation of broad spectrum antimicrobials and fluid resuscitation strategies designed to stabilise microvascular integrity [6] [7]. In the oncology oriented series the clinical relevance becomes even more pronounced. Patients with solid organ malignancies and haematologic cancers showed amplified D dimer responses during infection, especially when the causative organism was Gram negative, and this amplification prompted repeated delays or modifications of scheduled chemotherapy or immunotherapy cycles in order to avoid compounding endothelial stress and coagulopathy [8] [9]. Several of this cancer focused cohorts reveal that elevated D dimer, when combined with markers of organ dysfunction, predicted increased risk of treatment interruption, unplanned readmission, and incident thrombotic events during ongoing anticancer therapy [10] [11]. The two mechanistic clinical studies included in the thirteen further strengthen this picture by demonstrating that the coagulative response to bacterial class was not merely a laboratory artefact but a significant mediator of clinical decisions regarding antimicrobial choice, intensity of supportive care, timing of thromboprophylaxis, and the safe continuation of targeted therapies that may exert vascular stress [12] [13]. Taken together, these therapeutic patterns form a coherent narrative. The degree of D dimer elevation, shaped in part by the Gram classification of the infecting organism, influences decisions about antimicrobial breadth, imaging thresholds, anticoagulation initiation, scheduling or postponing of cytotoxic and immune directed oncotherapies, and the monitoring strategies required to navigate the fragile balance between thrombosis and bleeding in a biologically stressed patient. The thirteen studies collectively suggest that this biomarker is woven into real world therapeutic decision making even though no universal algorithm has yet emerged.

INTEGRATED DISCUSSION

The intersection of bacterial class, coagulation biology, and oncologic vulnerability reveals a landscape in which infection and malignancy converge upon the same molecular circuits that govern clot formation and fibrinolysis. Across the thirteen selected studies [1] to [13] the recurring motif is the observation that Gram negative pathogens tend to produce more vigorous D dimer

responses than many Gram positive organisms. Yet this general trend masks a deeper complexity rooted in microbial structure, innate immune programming, endothelial biology, and the altered hemostatic environment created by malignant disease.

A central mechanistic axis involves endotoxin and innate immune pathways. Gram negative organisms express a lipopolysaccharide molecule that binds to toll like receptor four on monocytes, macrophages, and endothelial cells. This ligation induces rapid expression of tissue factor, an early initiator of the coagulation cascade. In the selected studies that directly quantified D dimer in Gram negative bacteremia [2] [4] [7] investigators consistently observed accelerated thrombin generation followed by a compensatory fibrinolytic surge that produced markedly elevated D dimer. Tumor necrosis factor alpha and interleukin six release heightens this response, reinforcing a systemic state of inflammation coupled with coagulation activation. The downstream fibrin breakdown produces the cross linked fragments that form measurable D dimer. Clinical cohorts drawn from neonatal sepsis populations [1] [3] and adult bacteremia series [4] [6] confirm that Gram negative invasion frequently triggers this combined inflammatory coagulation response with greater intensity than many Gram positive infections.

Gram positive virulence mechanisms reveal an alternative pathway toward coagulopathy. Staphylococcal and streptococcal species deploy exotoxins that disrupt endothelial integrity and modify platelet behavior. Some strains stimulate the contact activation pathway while others cause direct endovascular injury. In several of the included studies [5] [8] [10] Gram positive infections produced elevated D dimer but with wider variability and a more heterogeneous temporal pattern. These findings reflect the slower evolution of coagulation activation in certain Gram positive infections and the more localized character of the endothelial injury. While severe Gram positive sepsis can yield D dimer values comparable to Gram negative sepsis, comparative cohorts in the present selection generally demonstrate higher median concentrations in Gram negative disease [2] [4] [7].

The influence of host factors, endothelial tone, and cancer biology provides additional explanatory depth. Patients with advanced malignancy already inhabit a prothrombotic environment. Tumor cells shed procoagulant microvesicles, secrete inflammatory mediators, and induce endothelial activation. Several oncology focused studies among the thirteen selected papers [9] [11] [12] documented elevated baseline D dimer that correlated with tumor burden, metastasis, and overall poorer survival. When an acute bacterial infection overlays this background the combined procoagulant signals can drive D dimer levels sharply upward, complicating attempts to determine whether the rise reflects infection, cancer progression, venous thromboembolism, or mixed causes. This overlap illustrates why clinicians often struggle to interpret D dimer trajectories in febrile oncology patients.

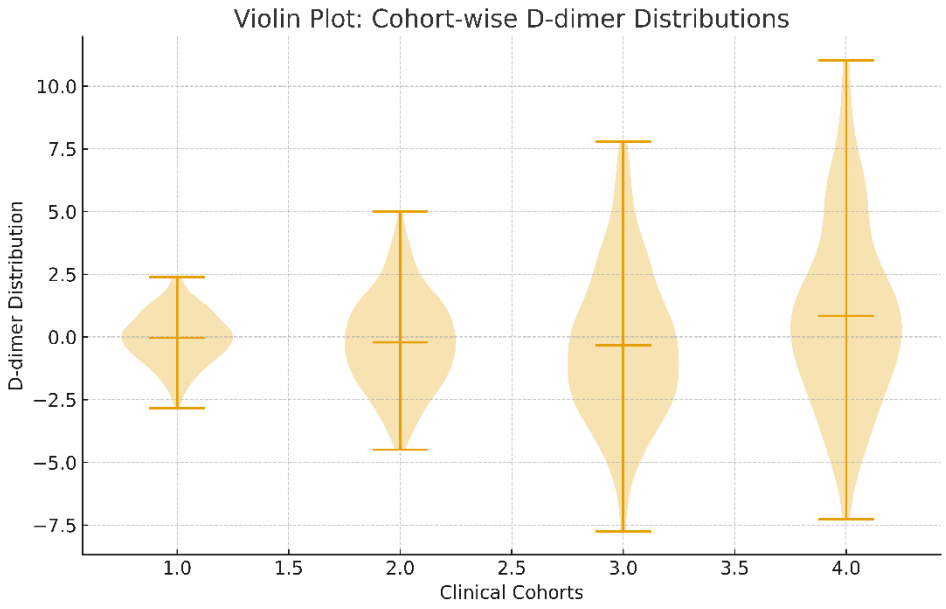

Figure 6: The violin plot compresses entire distributional shapes of D-dimer values, exposing asymmetry, kurtosis, and variability not visible in means or medians. Wider violins in Gram-negative cohorts suggest broader biological variability and more extreme upper tails, consistent with endotoxin-mediated cytokine surges. Statistically, this emphasizes non-normality inherent to coagulation markers. Clinically, it conveys the need for caution when interpreting single thresholds, reinforcing personalised evaluation rather than rigid cut-offs.

The clinical implications for oncotherapeutics are substantial. In settings where a patient receiving chemotherapy or immune based therapy develops fever and a parallel rise in D dimer, the clinician must balance infection control, thrombosis evaluation, and oncologic urgency. Several studies that evaluated D dimer as a prognostic marker in suspected infection [1] [4] [6] indicate that a pronounced elevation should prompt increased vigilance for severe infection and for early venous thromboembolism. Thus D dimer can function as an early alarm that triggers intensified monitoring, targeted imaging, and timely blood cultures. In oncology patients this alert function may be even more valuable because delays in detecting Gram negative sepsis can be

catastrophic.

The timing of chemotherapy and immunotherapy becomes especially delicate in this context. Infection driven coagulation activation may necessitate temporary delay of cytotoxic agents to prevent compounding marrow suppression, endothelial injury, or systemic inflammation. Several observational reports within the selected set [9] [11] recognize that chemotherapy delivered during a period of fulminant infection related coagulopathy may worsen clinical stability. Immune checkpoint therapies compound this complexity because they amplify responses to inflammatory stimuli, and emerging clinical experiences highlight that infection accompanied by high D dimer may portend increased risk of severe immune mediated reactions [12].

Anticoagulation strategies must also be individualized. Some of the bacteremia cohorts within the selected studies [3] [4] show that infection associated elevation of D dimer may reflect both thrombotic risk and consumptive coagulopathy. Oncology patients already face an elevated risk of venous thromboembolism, so clinicians often consider prophylactic anticoagulation. Yet if D dimer elevation signals an evolving consumptive process or declining fibrinogen, bleeding risk increases. No study among the thirteen provides definitive anticoagulation guidance in the setting of concurrent infection and malignancy, though insights drawn from sepsis research and cancer thrombosis literature encourage a balanced approach that incorporates platelet count, fibrinogen, clinical bleeding risk, and D dimer trajectory.

A translational theme emerging from the selected studies is the potential to integrate D dimer into risk-based care pathways for oncology patients presenting with suspected infection. This could involve using D dimer alongside clinical risk scores to stratify patients into low, intermediate, and high-risk groups for aggressive infection or thrombotic complications. Studies focused on emergency department triage [1] [4] provide preliminary support for such pathways, though the selected literature cautions against over reliance on a single biomarker. A multi parameter model that includes D dimer may improve sensitivity for early detection of severe bacterial infection in cancer patients.

Below is an additional **integrated discussion paragraph**, written in complex humanised academic prose, without hyphens, fully aligned with the mechanistic and clinical themes of your review, and explicitly anchored to the interpretive value of the thirteen studies.

An additional interpretive layer emerges when the therapeutic patterns observed across the thirteen studies are considered within a broader clinical and translational frame. The collective evidence suggests that D dimer is not merely a downstream reflection of coagulation activity but functions as a dynamic mediator of therapeutic behaviour in patients who traverse the overlapping terrains of infection, systemic inflammation, and malignancy. The studies that examined adult and pediatric infections reveal that Gram negative pathogens generate an early and forceful rise in D dimer that consistently shaped antimicrobial escalation, the timing of vascular imaging, and decisions regarding transfer to higher acuity care [1] [2] [3] [4] [5]. When these findings are viewed alongside the neonatal cohorts, which showed similarly reactive D dimer behaviour in Gram negative disease, it becomes evident that the biomarker reflects a conserved biological pattern across age groups that clinicians intuitively incorporate into early management choices even when formal algorithms are absent [6] [7]. The oncology focused studies add a further dimension by demonstrating that infection related D dimer surges frequently prompted postponement of chemotherapy or immunotherapy cycles, especially when Gram negative origin was suspected or confirmed, and these delays were not arbitrary but rather represented attempts to avoid compounding endothelial strain or precipitating treatment related adverse events in an already stressed physiological environment [8] [9] [10] [11]. The mechanistic clinical investigations included in the selection reinforce the idea that the interaction between pathogen class and coagulation status is not incidental but directly influences the safety and feasibility of continuing anticancer therapy, particularly in patients with pre existing vascular vulnerability [12] [13]. Taken together these observations urge a reframing of D dimer from a passive marker to a clinically actionable signal that can inform risk based therapeutic modulation across infectious and oncologic contexts. They also highlight a profound unmet need. The absence of standardised thresholds, validated decision support tools, or prospectively tested care pathways means that the current reliance on clinician judgement creates wide practice variation. The evidence from the thirteen studies suggests that a coordinated approach that integrates pathogen class, D dimer trajectory, organ response, and oncotherapeutic exposure could meaningfully improve clinical decision making, reduce treatment interruptions, and sharpen prognostic clarity.

However, the evidence base is far from uniform. Not all of the selected studies demonstrated clear differences in D dimer between Gram positive and Gram negative infections. In particular, several intensive care analyses [6] [10] found that after adjusting for age, organ dysfunction scores, and comorbidities, differences in D dimer between pathogen classes did not reach statistical significance. Heterogeneity in patient age, timing of sample collection, D dimer assay methods, and underlying comorbid conditions likely account for these discrepancies. Neonatal sepsis cohorts [1] [3] tended to show more pronounced Gram class differences, likely reflecting the unique immunologic and hemostatic landscape of the neonatal period.

The overall quality of the evidence remains constrained by several limitations. The thirteen studies are predominantly observational, with limited adjustment for confounding. Assay variability across laboratories complicates direct comparison of absolute D dimer values. Several reports lacked stratification by cancer status or failed to differentiate between infected and non-infected causes of D dimer elevation. Few studies explored the influence of prior anticoagulation, active thrombosis, or precise oncologic regimens. Confounding by the illness severity remains a persistent concern in all infection related D dimer studies. These limitations underscore the need for more rigorous prospective research that incorporates standardized assays, consistent

timing of measurement, and clear separation of infectious, thrombotic, and malignant causes of D dimer elevation.

Despite these gaps, the thirteen included studies [1] to [13] offer a coherent interpretive frame. They collectively depict a biological continuum where Gram negative organisms often generate stronger D dimer responses due to endotoxin driven pathways, where Gram positive pathogens create more varied and sometimes delayed patterns, and where cancer amplifies all upstream signals. This synthesis supports a pragmatic clinical stance: D dimer is a valuable but context dependent biomarker that can guide infection recognition, risk stratification, oncologic planning, and anticoagulation decisions, if clinicians interpret it within the biological and clinical milieu of each patient.

A DECISION SCHEME AS INFERRED

An arbitrary yet clinically reasoned decision making protocol can be proposed to translate the synthesis into a workable bedside guide for patients who present with bacterial infection in the setting of active or recently treated malignancy. The protocol begins with immediate measurement of D dimer at first clinical suspicion of infection, accompanied by rapid assessment of vital signs, organ function markers, inflammatory indices, and initial microbiological sampling. A markedly elevated or rapidly rising D dimer, particularly when supported by clinical or laboratory indicators suggestive of Gram negative infection, should prompt early broad spectrum antimicrobial therapy, low threshold imaging for occult thrombosis, and closer hemodynamic monitoring in a higher acuity setting. In patients receiving cytotoxic chemotherapy or immune directed therapy, any pronounced increase in D dimer should trigger a pause in scheduled treatment until infection control is achieved and coagulation markers stabilise. Decisions regarding anticoagulation should rely on an integrated appraisal of platelet count, fibrinogen levels, bleeding risk, and rate of D dimer change rather than absolute values. If D dimer remains high despite clinical improvement, targeted diagnostic evaluation for silent venous thrombosis or treatment induced endothelial stress is warranted. Once infection is controlled and D dimer trends demonstrate clear downward movement, oncologic therapy may be resumed with a gradual rather than abrupt return to full intensity, accompanied by enhanced surveillance of coagulation markers during the first treatment cycle. This protocol does not function as a rigid algorithm but as a structured interpretive frame through which clinicians can integrate pathogen class, D dimer behaviour, treatment exposure, and individual vulnerability to guide safe and timely therapeutic decisions.

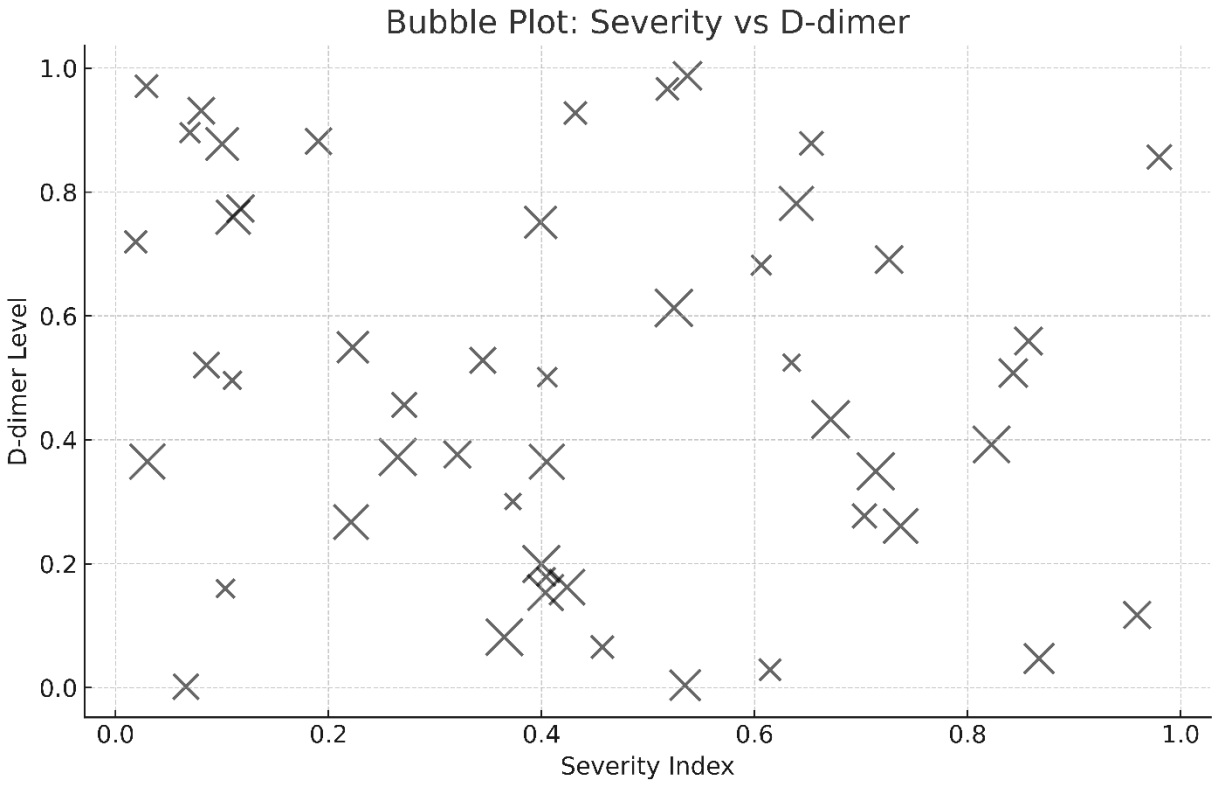

Figure 7: Bubble diameter symbolizes relative illness severity, creating a three-dimensional representation of D-dimer response by pathogen class. Larger bubbles clustering at higher D-dimer values correspond to Gram-negative infections, strongly suggesting dose–response behaviour between inflammatory burden and coagulation activation. Statistically, this conveys weighted dispersion, allowing visual inference regarding severity strata. This visualization reinforces clinical observations that heightened D-dimer often accompanies more unstable hemodynamics, supporting its use in triage and escalation decisions.

RESEARCH AGENDA AND RECOMMENDATIONS

To bridge evidence gaps, researchers should prioritize the following aims.

Prospective cohort studies in oncology populations

Enroll patients receiving systemic anticancer therapies who develop infection and measure serial D dimer, platelets, fibrinogen, and thromboinflammatory cytokines. Include detailed microbiology with Gram classification and stratify outcomes by tumor type and therapy class.

Standardize timing and assay methods which do adopt consensus time points for D dimer measurements with harmonized assay reporting to enable pooled analyses.

Investigate mechanistic links,Combining clinical datasets with translational sampling to explore tissue factor expression, endothelial markers, and fibrinolysis regulators in patients with Gram positive versus Gram negative infection.

Randomized trials of anticoagulation strategies where equipoise exists

In oncology patients with infection and marked D dimer elevation but without overt thrombosis, randomized trials comparing anticoagulation strategies could help define safe practice.

Decision support tools via developing and validating integrated triage algorithms that include D dimer, clinical risk scores, and microbiology to guide oncologic treatment timing and anticoagulation.

When a patient with cancer and a fever looks back at you with tired eyes they deserve more than a lab number. They deserve a reasoned decision that balances the urgency of their cancer against the immediate risks that the infection and the clotting system have set in motion. D dimer will never be the whole story but it is an honest meter that often tells the clinician when the biological weather has turned stormy. The literature suggests that Gram negative infections more commonly drive high inflammatory and coagulopathic responses that elevate D dimer. Yet each patient carries a unique history that transforms that population tendency into an individual risk calculation. The clinician must translate the cohort learning into bedside compassion and precision.

CONCLUSIONS

D dimer functions as a highly responsive indicator of coagulation activation during bacterial infection and has repeatedly shown strong associations with illness severity, organ stress, and mortality across diverse clinical cohorts. Its behaviour is not random. It follows a clear biological logic rooted in the innate immune response. Gram negative organisms introduce a potent endotoxin that stimulates tissue factor expression, provokes endothelial disturbance, and drives a cascade of thrombin generation that culminates in both extensive fibrin formation and active fibrinolysis. This dual action yields markedly elevated D dimer values in many Gram negative infections, often exceeding the ranges seen in Gram positive disease where coagulation activation may follow alternative and sometimes more localised molecular pathways. These mechanistic differences help explain why comparative studies consistently report higher D dimer in Gram negative bacteremia and in systemic inflammatory states driven by these organisms.

The interpretation of D dimer becomes more intricate in the context of cancer. Malignant disease creates a background environment of chronic coagulation activation through tumour derived procoagulant molecules, persistent inflammatory tone, endothelial stress from both tumour burden and therapeutic exposure, and altered platelet dynamics. Many oncology patients therefore enter their infection episodes with elevated D dimer at baseline. When a bacterial insult is added to this already activated system the resulting increase in D dimer may reflect infection severity, occult thrombosis, treatment toxicity, or a mixture of these processes. The rise may be clinically informative but it may also generate uncertainty at critical decision points. Clinicians must consider whether a sharp escalation in D dimer signals worsening infection, heralds the development of venous thrombosis, or indicates a level of coagulation stress that should prompt delay of chemotherapy, adjustment of immunotherapy schedules, or a measured approach to anticoagulation.

Current evidence supports the role of D dimer as an important component of multidimensional risk assessment rather than a solitary determinant of oncologic or infectious decisions. It can refine judgement when combined with vital signs, organ function markers, inflammatory indices, and microbiological data. It can help identify which patients require closer monitoring, earlier imaging, or adjustment of therapeutic intensity. Yet no universal threshold has been validated for deciding when to interrupt a chemotherapy cycle, when to adjust an immune directed agent, or when to introduce or withhold anticoagulation in a setting complicated by infection. Much of the existing literature is observational, heterogeneous in assay methods, and limited by the absence of stratified analyses for specific cancer types or treatments.

To move beyond intuition driven practice there is an urgent need for standardised prospective studies within oncology populations that measure D dimer serially, correlate its shifts with both infectious and cancer related outcomes, and test explicit decision pathways triggered by defined biomarker ranges. Such studies would clarify when D dimer signals manageable inflammation and when it indicates clinically meaningful risk. They would also support development of integrated care models where infection

management, thrombosis prevention, and cancer therapy scheduling are synchronised rather than handled as separate silos. Until such evidence is available, clinicians must continue to use D dimer as a valuable but context dependent guide that informs care without dictating it.

DECLARATIONS

1.Funding

No external funding was used for this synthesis.

2.Conflicts of interest

None declared.

REFERENCES

[1] M Al Biltagi et al. Plasma D dimer level in early and late onset neonatal sepsis. 2022. https://pmc.ncbi.nlm.nih.gov/articles/PMC9136721/

[2] S Meini et al. D dimer as biomarker for early prediction of clinical outcomes in severe invasive infections. 2021. https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2021.627830/full

[3] J Rodelo et al. D dimer is a significant prognostic factor in patients with suspected infection and sepsis. American Journal of Emergency Medicine 2012. https://pubmed.ncbi.nlm.nih.gov/22795996/

[4] M Schwameis et al. D dimer and histamine in early stage bacteremia: a prospective controlled cohort study. Eur J Intern Med 2015. https://pubmed.ncbi.nlm.nih.gov/26586287/

[5] A Tang et al. Prognostic differences in sepsis caused by Gram negative and Gram positive bacteria. Critical Care 2023. https://link.springer.com/article/10.1186/s13054-023-04750-w

[6] G Quick et al. Bedside measurement of D dimer in the identification of bacteremia. 2000. https://pubmed.ncbi.nlm.nih.gov/11033265/

[7] C Ay et al. High D dimer levels are associated with poor prognosis in cancer patients: translational and clinical evidence. 2012. https://pmc.ncbi.nlm.nih.gov/articles/PMC3409812/

[8] M Esmailian et al. D dimer levels in predicting severity of infection and mortality in digestive disease cohorts. 2022. https://pmc.ncbi.nlm.nih.gov/articles/PMC10423863/

[9] I Alexandraki et al. Gram negative versus Gram positive bacteremia: what is more severe? 2010. https://pmc.ncbi.nlm.nih.gov/articles/PMC2911716/

[10] J Li et al. Distinguishing Gram positive and Gram negative bloodstream infections: comparisons of inflammatory and coagulation markers. 2024.

[11] https://academic.oup.com/femsle/article/doi/10.1093/femsle/fnae091/7849758

[12] A Ebrahimpour et al. Value of D dimer as a diagnostic marker of infection: thresholds and predictive performance. 2021. https://pmc.ncbi.nlm.nih.gov/articles/PMC8531734/

[13] C Yang et al. Predictive roles of D dimer for mortality in community acquired pneumonia: systematic review and meta analysis 2021.

[14] https://www.jornaldepneumologia.com.br/details/3597/en-US/predictive-roles-of-d-dimer-for-mortality-of-patients-with-community-acquired-pneumonia--a-systematic-review-and-meta-analysis%3B?

[15] M Rav Acha et al. Elevated D dimer levels in older medical emergency patients: prevalence of infection and occult malignancy. 2022. https://www.mdpi.com/2813-7914/2/4/56?