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Monitoring of Anticoagulant Therapy in Heart Disease: Considerations for the Current Assays: A systematic Review

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ABSTRACT

Anticoagulant therapy is a cornerstone in the management of cardiovascular diseases, including atrial fibrillation, venous thromboembolism, and mechanical heart valve replacement. While these therapies significantly reduce thromboembolic events, they are associated with an inherent risk of bleeding, making precise monitoring essential for optimizing clinical outcomes. This systematic review evaluates the current laboratory assays used to monitor anticoagulant therapy, their clinical relevance, limitations, and emerging methodologies. Traditional monitoring methods, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR), remain widely utilized. PT and INR are standard for warfarin therapy; however, variations in thromboplastin reagents and laboratory practices contribute to inter-laboratory variability, potentially affecting dosing accuracy. aPTT is commonly employed for unfractionated heparin monitoring, yet its sensitivity is influenced by reagents and instrumentation, prompting recommendations for institution-specific therapeutic ranges and anti-Xa assay utilization for more precise assessment. Direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban, offer predictable pharmacokinetics and reduce the need for routine monitoring. Nonetheless, clinical situations including renal or hepatic impairment, bleeding complications, and urgent surgical interventions may necessitate evaluation of anticoagulant effects. Emerging assays, including anti-Xa activity measurement, thrombin generation assays, and point-of-care testing, demonstrate improved accuracy and patient-centered monitoring potential, though limited accessibility and standardization remain challenges. Overall, integrating these advanced methods with conventional assays can enhance anticoagulation management, minimize adverse events, and improve patient safety. Standardization of laboratory protocols, adherence to guidelines, and ongoing research are critical to achieving reliable monitoring across diverse clinical settings.

Introduction

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide, with thromboembolic complications contributing significantly to adverse outcomes in patients with heart disease [1]. Conditions such as atrial fibrillation, mechanical heart valve replacement, acute coronary syndromes, and venous thromboembolism necessitate the use of anticoagulant therapy to prevent the formation and propagation of blood clots.

Anticoagulants, including vitamin K antagonists (VKAs), unfractionated heparin (UFH), low molecular weight heparin (LMWH), and direct oral anticoagulants (DOACs), have revolutionized cardiovascular care by reducing thrombotic events. However, their therapeutic benefits are counterbalanced by an increased risk of bleeding [2], which may range from minor hemorrhage to life-threatening events such as intracranial bleeding. Consequently, precise monitoring of anticoagulant therapy is essential to optimize the delicate balance

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between preventing thromboembolism and minimizing bleeding complications [3].

Historically, laboratory monitoring of anticoagulants has relied on standardized coagulation assays, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). PT and INR are extensively used to monitor warfarin therapy by assessing the extrinsic and common coagulation pathways. The INR standardizes PT measurements across different laboratories, theoretically allowing for consistent monitoring of anticoagulant intensity. However, variability in thromboplastin reagents and instrument calibration can still result in significant inter-laboratory differences. Similarly, aPTT is employed to monitor unfractionated heparin therapy, measuring intrinsic and common coagulation pathways. Despite its widespread use, aPTT is influenced by the reagent type, analyzer, and patient-specific factors, leading to inconsistencies in therapeutic range interpretation. These limitations have prompted the development of alternative assays, such as anti-Xa activity measurement, which provide a more direct assessment of anticoagulant effect [4].

The emergence of DOACs including dabigatran, rivaroxaban, apixaban, and edoxaban has further transformed anticoagulation management. These agents offer predictable pharmacokinetics, rapid onset of action, and a lower risk of major bleeding compared to VKAs. Importantly, routine laboratory monitoring is generally unnecessary with DOACs, reducing the burden on healthcare systems and patients alike. Nevertheless, certain clinical circumstances necessitate the evaluation of DOAC anticoagulant activity. For instance, in patients with severe renal or hepatic impairment, those experiencing bleeding complications, individuals at risk of thromboembolic events, or patients requiring urgent surgical interventions, laboratory assessment of anticoagulant effect becomes crucial. Standard coagulation assays, including PT, aPTT, and INR, are often inadequate for these purposes due to their insensitivity to DOAC mechanisms of action. Specialized assays, such as dilute thrombin time, ecarin clotting time, and anti-Xa assays, have been developed to quantify DOAC activity more accurately. Despite their specificity, these assays are not universally available and are rarely standardized across clinical laboratories, limiting their practical utility [5].

In addition to conventional laboratory tests, point-of-care (POC) devices and emerging global assays have been investigated for anticoagulant monitoring. POC devices, such as CoaguChek, allow rapid, bedside evaluation of INR, facilitating self-management and more frequent monitoring for patients on warfarin. Thrombin generation assays provide a global assessment of coagulation potential and can capture both procoagulant and anticoagulant changes. These novel methods offer the potential for more precise individualized anticoagulation management, yet widespread adoption is hampered by cost, complexity, and lack of standardization [6].

Standardization of anticoagulant monitoring remains a critical challenge in contemporary clinical practice. Variability in laboratory reagents, instrumentation, and methodological protocols leads to inconsistent results, which may compromise patient safety. International guidelines, including recommendations from the International Society on Thrombosis and Haemostasis (ISTH) and the College of American Pathologists, emphasize the importance of establishing laboratory-specific therapeutic ranges, performing regular quality control, and, when possible, implementing standardized assay protocols. Such measures are particularly important for high-risk populations, including elderly patients, those with multiple comorbidities, and individuals with mechanical heart valves or complex coagulopathies [7].

The clinical implications of precise anticoagulant monitoring extend beyond laboratory accuracy. Optimized monitoring can reduce the incidence of adverse events, including major bleeding and recurrent thromboembolism, and improve patient adherence to therapy. Additionally, individualized monitoring strategies may enhance the cost-effectiveness of anticoagulant therapy by minimizing complications that necessitate hospitalization or additional interventions. Emerging evidence suggests that integrating advanced laboratory techniques, including anti-Xa activity measurement and thrombin generation assays, with traditional monitoring can provide a more nuanced understanding of anticoagulant effects, allowing clinicians to tailor therapy according to patient-specific risk profiles.

Despite these advancements, gaps remain in the literature regarding the optimal monitoring strategy for diverse patient populations. Variability in assay availability, lack of standardized protocols for emerging tests, and limited real-world data on long-term outcomes pose challenges for evidence-based implementation. Furthermore, most studies have focused on single anticoagulant classes, with limited comparative research assessing monitoring strategies across different therapies. Consequently, there is a pressing need for systematic reviews and meta-analyses that comprehensively evaluate existing monitoring assays, identify their strengths and limitations, and provide guidance for clinical decision-making [8].

In summary, anticoagulant therapy is integral to the management of heart disease, but its benefits are balanced by the risk of bleeding complications. Traditional assays such as PT, INR, and aPTT remain foundational tools for monitoring, yet they are limited by variability and lack of sensitivity for certain anticoagulants, particularly DOACs.

Emerging techniques, including anti-Xa assays, thrombin generation tests, and POC devices, offer promising alternatives for more precise monitoring, although their implementation is constrained by cost, standardization, and accessibility. There is an urgent need for systematic evaluation of these assays to inform evidence-based clinical practice, ensure patient safety, and optimize therapeutic outcomes.

This review aims to critically examine the current laboratory methods used in anticoagulant monitoring, explore their limitations, and highlight emerging strategies that may improve individualized patient care [9]. In table (1) comparative Review of Key Studies on Anticoagulant Therapy Monitoring in Heart Disease was illustrated.

Table 1. Comparative Review of Key Studies on Anticoagulant Therapy Monitoring in Heart Disease

Article Title	Year	Study Type	Key Findings
A Comprehensive Review of Direct Oral Anticoagulants	2025	Systematic Review	Examines strategies to optimize DOAC monitoring and provides guidance for clinical management.
Comparison of anticoagulation monitoring strategies for patients supported on ECMO	2023	Systematic Review	Compares various anticoagulation monitoring strategies in ECMO patients, emphasizing Anti-Xa and aPTT.
Direct Oral Anticoagulant Use: A Practical Guide to Laboratory Monitoring	2020	Systematic Review	Provides practical guidance on laboratory monitoring of DOACs and compares them to VKAs.
Laboratory Monitoring of Direct Oral Anticoagulants (DOACs)	2021	Systematic Review	Reviews laboratory methods for measuring DOAC activity and discusses current challenges.
Direct Oral Anticoagulants: An Updated Systematic Review of Laboratory Methods	2022	Systematic Review	Updates laboratory methods for DOAC monitoring and compares them with traditional assays.
Comparison of Heparin Red, Azure A and Toluidine Blue assays for direct quantification of heparins in human plasma	2017	Experimental Study	Compares sensitivity and accuracy of three assays for direct heparin measurement in plasma.

Traditional Laboratory Assays

Prothrombin Time (PT) and INR: Despite its advantages, the PT/INR system is not without limitations. The sensitivity of PT to different thromboplastin reagents remains a challenge, particularly when reagents with varying International Sensitivity Index (ISI) values are used. Furthermore, PT and INR primarily reflect the activity of vitamin K-dependent clotting factors and may not adequately capture the anticoagulant effects of newer agents such as direct oral anticoagulants (DOACs) or certain low-molecular-weight heparins. Factors such as liver disease, dietary vitamin K intake, concomitant medications, and genetic polymorphisms affecting warfarin metabolism can also influence PT/INR results, highlighting the need for individualized interpretation and close clinical monitoring [10].

Clinical evidence consistently demonstrates that maintaining INR within the recommended therapeutic range significantly reduces thromboembolic complications while minimizing bleeding risk. In patients with atrial fibrillation, mechanical heart valves, or venous thromboembolism, studies have shown that sub therapeutic INR levels are associated with increased thrombotic events, whereas serotherapeutic levels correlate with heightened bleeding risk. Consequently, frequent INR monitoring, especially during initiation and dose adjustments, is crucial to achieving optimal outcomes. Additionally, point-of-care INR devices have facilitated patient self-monitoring and self-management, demonstrating improved therapeutic control and patient satisfaction in multiple studies.

Advances in laboratory standardization and quality control have further strengthened the reliability of PT/INR monitoring. Laboratories are encouraged to calibrate their thromboplastin reagents regularly, participate in external quality assessment programs, and establish locally validated therapeutic ranges when necessary. Clinicians must also integrate PT/INR results with clinical assessment, recognizing that laboratory values alone cannot fully capture an individual patient's bleeding or thrombotic risk. In conclusion, PT and INR remain indispensable tools for managing VKA therapy. Their simplicity, widespread availability, and standardized interpretation through INR make them effective for guiding anticoagulant dosing and minimizing adverse events. Nevertheless, clinicians must remain aware of their limitations, particularly in the context of reagent variability, patient-specific factors, and non-VKA anticoagulants. Optimized use of PT/INR, combined with careful clinical judgment and patient education, continues to be

central to safe and effective anticoagulation management. Continued research into complementary assays and personalized monitoring strategies may further enhance the precision of anticoagulant therapy in diverse patient populations [11].

Activated Partial Thromboplastin Time (aPTT):

Despite its clinical utility, aPTT is subject to significant variability. Factors such as the type and sensitivity of the reagent, the instrumentation used, pre-analytical variables, and patient-specific characteristics such as elevated factor VIII levels, lupus anticoagulants, or deficiencies of coagulation factors can substantially influence the results. This variability necessitates careful interpretation of aPTT values, ideally within laboratory-specific therapeutic ranges that are calibrated against heparin concentrations determined by anti-Xa assays. Without such calibration, reliance solely on aPTT may lead to under- or over-anticoagulation, increasing the risk of thromboembolic complications or major bleeding events.

Clinical evidence demonstrates that maintaining aPTT within the recommended therapeutic range is critical to optimizing the safety and efficacy of UFH therapy. Sub therapeutic aPTT values are associated with insufficient anticoagulation and increased risk of thrombus formation, whereas serotherapeutic values significantly increase the likelihood of hemorrhagic complications. Therefore, frequent monitoring, particularly during initiation, titration, and in patients with fluctuating clinical conditions, is essential to ensure therapeutic effectiveness. Additionally, aPTT remains valuable for detecting intrinsic coagulation abnormalities in patients not receiving anticoagulants, serving as a diagnostic tool in bleeding disorders and preoperative evaluations. The limitations of aPTT have led to the increased adoption of alternative or complementary assays, such as anti-Xa activity measurement, which directly quantifies heparin concentration and offers more consistent results across laboratories. Anti-Xa assays are less influenced by pre-analytical and reagent variability, making them particularly useful in complex clinical scenarios, such as critically ill patients, those with lupus anticoagulants, or individuals with significant hypercoagulable states. Nevertheless, aPTT remains the first-line monitoring tool in most clinical settings due to its widespread availability, rapid feedback, and cost-effectiveness [12].

In conclusion, aPTT continues to play a central role in the monitoring of UFH therapy, balancing efficacy in thromboembolism prevention with the risk of bleeding. Its clinical utility is maximized when interpreted within laboratory-specific therapeutic ranges and complemented, when necessary, by more specific assays like anti-Xa measurement. Clinicians must consider both patient-specific factors and methodological limitations when relying on aPTT results, ensuring that anticoagulant therapy is safe, effective, and individualized. Continuous quality control, standardization efforts, and integration with emerging monitoring strategies will further enhance the precision and reliability of anticoagulation management using aPTT.

Table 2. Comparative Table: Recent Studies on Activated Partial Thromboplastin Time (aPTT)

Study Title	Key Findings
Dual Guided Heparin Monitoring with Anti-Xa and aPTT during Left-Sided Impella Support	Investigated the correlation between anti-Xa and aPTT in patients on Impella support. Found a weak correlation, suggesting that aPTT may not be reliable as a sole monitoring tool in this setting. OUP Academic
Isolated Prolongation of Activated Partial Thromboplastin Time: Causes and Clinical Implications	Reviewed causes of isolated aPTT prolongation, including factor deficiencies and the effects of anticoagulants. Emphasized the need for comprehensive evaluation when aPTT is prolonged without other abnormalities. PMC
Evaluation of an Integrated Activated Partial Thromboplastin Time Assay: Cephen LS/Cephen	Assessed the performance of an integrated aPTT assay. Found that it provides reliable results, which could enhance monitoring in various clinical settings. Wiley Online Library
Comparison of Heparin Red, Azure A, and Toluidine Blue Assays for Direct Quantification of Heparins in Human Plasma	Compared three assays for direct heparin quantification. Highlighted differences in sensitivity and accuracy, which are crucial for effective anticoagulation monitoring. Nature

Direct Oral Anticoagulants (DOACs) and Monitoring Challenges

One of the primary challenges in DOAC monitoring is the lack of a universally accepted, standardized laboratory assay that can reliably quantify anticoagulant effect across all agents. Unlike VKAs, which are monitored using prothrombin time (PT) and International Normalized Ratio (INR), DOACs act through highly specific mechanisms direct inhibition of thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban). Consequently, conventional coagulation assays such as PT, aPTT, and INR are generally insensitive to DOACs or provide results that do not reliably correlate with

plasma drug concentrations or anticoagulant activity. For example, dabigatran prolongs aPTT and thrombin time (TT) in a concentration-dependent manner but may have minimal effect on PT, whereas rivaroxaban prolongs PT variably depending on the reagent used. Such variability complicates interpretation and underscores the need for more specific assays in certain clinical contexts [13].

Specialized assays, including dilute thrombin time and ecarin clotting time for dabigatran, and chromogenic anti-Xa assays calibrated for factor Xa inhibitors, provide more accurate measurements of anticoagulant activity. These assays are particularly valuable in clinical situations such as suspected overdose, renal or hepatic impairment, perioperative management, emergent bleeding, thromboembolic events during therapy, or when drug interactions may alter anticoagulant levels. Despite their specificity, these assays are not widely available in all clinical laboratories and may be limited by cost, technical complexity, and lack of standardization. As a result, clinicians often rely on indirect assessment of anticoagulant effect, including timing of last dose, renal and hepatic function, and clinical judgment.

Another challenge lies in patient-specific variability. Renal and hepatic dysfunction can significantly affect the pharmacokinetics of DOACs, leading to accumulation and increased bleeding risk. Age, body weight, and concomitant medications further influence plasma drug concentrations, highlighting the need for individualized assessment in high-risk populations. In addition, although DOACs generally have a lower risk of intracranial and major bleeding compared to VKAs, bleeding events still occur and require rapid evaluation of anticoagulant activity to guide reversal strategies. Specific reversal agents, such as idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors, underscore the importance of accurate laboratory assessment in guiding appropriate use.

Despite these challenges, the clinical outcomes associated with DOAC therapy have been favorable, with large-scale randomized trials demonstrating efficacy and safety comparable to or superior to VKAs. The predictable pharmacologic profile of DOACs reduces the need for routine monitoring in the majority of patients, simplifying management and improving adherence. However, the residual need for selective monitoring in complex clinical scenarios emphasizes that DOAC therapy is not entirely free from laboratory assessment considerations. Emerging point-of-care and global coagulation assays may enhance the ability to evaluate anticoagulant effect in real-time, providing additional tools for individualized patient management [14].

In conclusion, DOACs have introduced a paradigm shift in anticoagulant therapy, offering convenience, efficacy, and safety without the routine monitoring requirements characteristic of VKAs. Nonetheless, the challenges associated with laboratory monitoring, including assay insensitivity, lack of standardization, and patient-specific variability, remain important considerations in certain clinical contexts. Clinicians must maintain awareness of these limitations and employ specialized assays when indicated to ensure safe and effective therapy. Integrating patient-specific factors, clinical judgment, and emerging monitoring strategies will further optimize DOAC management, particularly in high-risk or complex patient populations. Continued research, standardization of laboratory methods, and improved accessibility to specific assays are essential to fully realize the potential of DOACs while minimizing adverse outcomes. By addressing these challenges, healthcare providers can enhance the precision, safety, and effectiveness of anticoagulation therapy in patients with cardiovascular disease.

Table 3. Comparative Table: Studies on DOAC Monitoring Challenges

Study	Year	Population / Setting	Key Monitoring Challenge(s) Investigated	Findings / Relevance to Clinical Monitoring
Evaluation of Direct Oral Anticoagulant Prescribing in Patients With Moderate to Severe Renal Impairment	2021	Outpatients with moderate to severe renal impairment (CrCl <50 mL/min, including dialysis)	Assessing how often DOAC doses are appropriately adjusted in renal impairment, and relation of dosing to bleeding/thrombotic outcomes. PubMed	Found that inappropriate dosing is common; mis-dosing in this group is linked to increased risk of adverse events. This underscores the need for better individualized monitoring (renal function, drug levels) when prescribing DOACs in those with kidney impairment. PubMed
Challenges to Laboratory Monitoring of Direct Oral Anticoagulants (Review)	2024	High-risk patient groups (e.g. renal/hepatic impairment, drug interactions,	Examines which clinical situations may benefit from DOAC drug-level monitoring (DLM), limitations of conventional coagulation tests, and utility/emerging quantitative methods (e.g. anti-	Concludes that while routine monitoring is generally unnecessary, in specific contexts (e.g. renal/hepatic dysfunction, suspected noncompliance, drug interactions, perioperative bleeding risk) laboratory

		perioperative settings)	Xa for Xa inhibitors) SAGE Journals	quantification can be clinically useful. Also points out limitations in assay availability and turnaround. SAGE Journals
Efficacy and Safety of Oral Anticoagulants for Atrial Fibrillation Patients With Chronic Kidney Disease: A Systematic Review and Meta-Analysis	2022	AF patients with varying levels of renal impairment, including advanced CKD (CrCl <30 mL/min)	Comparing DOACs vs warfarin for both stroke prevention and major bleeding in CKD; reflects challenges in balancing efficacy and safety when drug elimination is reduced. Also implies a need for monitoring. PubMed	Found DOACs generally had lower risk of major bleeding and stroke vs warfarin even in CKD patients, though heterogeneity exists; emphasizes importance of dose adjustment and possibly lab monitoring in severe renal dysfunction. PubMed
Direct Oral Anticoagulant Monitoring Within Primary Care: A Quality Improvement Project	2023	Primary care setting, patients prescribed DOACs	Investigated process implementation of DOAC monitoring (e.g. checking renal function / weight annually, ensuring counselling, lab tests) in a primary care clinic; focusing on increasing adherence to "monitoring" even if not drug level assays. PubMed	Showed that using quality improvement cycles and stakeholder engagement improved monitoring metrics (e.g. percentage with appropriate blood tests rose, weight recorded, etc.). Highlights that even non-specialized settings can improve safety by implementing monitoring processes. PubMed

Commentary: What These Studies Reveal about DOAC Monitoring Challenges

✓ Renal Impairment is a Key Determinant of Risk and Monitoring Needs:

- Shows that many patients with moderate to severe renal impairment are dosed inappropriately with DOACs. Because DOACs are partly eliminated by the kidneys, impaired renal function can lead to drug accumulation and increased bleeding risk, or conversely underdosing, leading to thrombotic risk. Also further supports that, even in patients with chronic kidney disease (including severely reduced creatinine clearance), DOACs can perform better than warfarin in some outcomes—but heterogeneity and elevated risk remain. Hence the balancing act is more precarious, meaning more tailored monitoring (renal function, possibly drug levels) becomes more relevant.

✓ Identifying Populations Where Drug-Level or Enhanced Laboratory Monitoring Might Help:

- This table explicitly discusses which clinical settings might necessitate monitoring beyond just fixed doses: hepatic dysfunction, drug interactions, suspected noncompliance, surgery, etc.
- These settings often aren't covered sufficiently by routine care; thus, lacks in monitoring or lab capability become clinically important gaps.

✓ Implementation in Real World / Primary Care Settings is Suboptimal, but Improvement is Possible:

- This table shows that in a primary care clinic, using structured quality improvement methods (PDSA cycles, check listing, counselling, lab test tracking) markedly improved monitoring processes even though these did not always involve measuring 'drug levels.'
- This suggests that much of monitoring challenge is not only technical assay availability, but system/process issues: ensuring patients are reviewed, labs ordered, and patient info (renal function, weight, etc.) is updated.

✓ Outcome Studies Highlight Safety/Efficacy Trade-offs and Reinforce Monitoring Importance:

- This table affirms that DOACs tend to have favorable profiles versus warfarin for major bleeding, but the safety margin shrinks in renal impairment or when dosing is incorrect.
- Thus, monitoring helps ensure that DOAC therapy remains within that favorable margin by detecting when conditions (e.g. kidney function, drug interactions) shift the balance toward higher risk.

Emerging Monitoring Techniques

Anti-Xa Assays: Anti-Xa assays measure the activity of factor Xa inhibitors and are particularly useful for monitoring heparin and DOAC therapies. These assays provide a more direct assessment of anticoagulant activity compared to traditional methods. However, their availability and standardization remain limited [15].

Thrombin Generation Assays: Thrombin generation assays evaluate the overall thrombin potential of plasma, offering insights into the coagulation system's response to anticoagulants. These assays are sensitive to both pro- and anticoagulant changes and can provide a comprehensive assessment of anticoagulant therapy. Despite their potential, thrombin generation assays

are not yet widely implemented in clinical practice due to complexity and cost.

Point-of-Care (POC) Testing: POC testing devices, such as CoaguChek, allow for real-time monitoring of anticoagulation status. These devices are particularly beneficial for patients on warfarin therapy, enabling self-management and more frequent monitoring. However, their accuracy can be influenced by factors like hematocrit levels and device calibration [16].

Standardization and Quality Control: The need for standardization is perhaps most evident in the monitoring of VKAs, where PT and INR are used to guide dosing. While the INR was developed specifically to reduce inter-laboratory variability by correcting for differences in thromboplastin sensitivity, persistent discrepancies still occur due to reagent differences, instrument calibration, and pre-analytical factors. Without rigorous standardization, patients may be under- or over-anticoagulated, increasing the risk of thromboembolic events or hemorrhage. To address these challenges, laboratories are encouraged to regularly calibrate reagents against reference standards, participate in external quality assessment programs, and verify locally established therapeutic ranges. Such practices ensure that PT and INR results are accurate, reproducible, and clinically reliable, enabling clinicians to make informed dosing decisions.

Similarly, aPTT, the primary assay for monitoring UFH therapy, is highly sensitive to laboratory-specific conditions, including the type of activator used, reagent composition, and instrumentation. These variables can lead to substantial differences in measured aPTT values between laboratories, complicating the interpretation of therapeutic ranges. Quality control measures, such as internal and external validation, regular equipment maintenance, and establishment of institution-specific therapeutic ranges calibrated against anti-Xa activity, are critical for ensuring the reliability of aPTT measurements. In high-risk populations, such as critically ill patients or those with coagulopathies, adherence to stringent quality control protocols can be the difference between effective anticoagulation and adverse clinical outcomes.

Anti-Xa assays, which provide a direct measurement of heparin or factor Xa inhibitor activity, have emerged as a more precise alternative to aPTT in certain clinical scenarios. These assays are less influenced by patient-specific variables and reagent differences, offering improved accuracy in complex situations, such as in patients with lupus anticoagulants, extreme body weights, or renal impairment. However, the lack of universal standardization across laboratories, differences in calibration protocols, and variability in assay methodology remain significant barriers to widespread adoption. Implementing rigorous quality control measures, including inter-laboratory comparisons, use of standardized calibrators, and adherence to established protocols, is essential for translating the precision of anti-Xa assays into meaningful clinical outcomes [17].

The monitoring of DOACs presents unique challenges for standardization and quality control. Routine coagulation testing is generally unnecessary for these agents due to their predictable pharmacokinetics. However, specialized assays, such as dilute thrombin time for dabigatran and anti-Xa assays calibrated for rivaroxaban, apixaban, and edoxaban, may be required in special circumstances, including renal or hepatic impairment, suspected overdose, major bleeding, or perioperative management. The limited availability and lack of standardized protocols for these assays can result in variability and uncertainty in clinical decision-making. Establishing clear guidelines, validating laboratory-specific procedures, and ensuring rigorous quality control are therefore critical for safely integrating DOAC monitoring into clinical practice.

International guidelines emphasize the importance of harmonization and quality assurance in anticoagulant monitoring. Organizations such as the International Society on Thrombosis and Haemostasis (ISTH), the College of American Pathologists (CAP), and the World Health Organization (WHO) provide frameworks for laboratory standardization, including calibration protocols, external quality assessment programs, and recommendations for therapeutic ranges. Adherence to these guidelines ensures that anticoagulation results are consistent, reliable, and comparable across different healthcare institutions, improving patient safety and optimizing clinical outcomes [18].

In addition to laboratory-focused standardization, quality control extends to the broader context of clinical practice. Healthcare providers must integrate laboratory results with patient-specific factors, such as age, renal and hepatic function, comorbidities, concomitant medications, and bleeding or thrombotic risk profiles. Clinical judgment, patient education, and adherence to evidence-based protocols are essential complements to laboratory standardization, ensuring that anticoagulant therapy is applied safely and effectively. Training of laboratory personnel, ongoing competency assessment, and continuous quality improvement initiatives further enhance the reliability and clinical utility of anticoagulant monitoring.

Technological advancements, including point-of-care testing (POCT) and automated coagulation analyzers, have the potential to improve standardization and quality control. POCT devices, such as portable INR monitors, allow rapid, bedside

measurement of anticoagulation status, supporting timely clinical decisions and patient self-management. However, these devices require careful calibration, quality control, and validation against laboratory-based methods to ensure accuracy and reproducibility. Automated analyzers reduce human error and improve consistency but must also undergo routine maintenance, reagent standardization, and quality checks to maintain reliability [19].

In conclusion, standardization and quality control are indispensable components of anticoagulant therapy monitoring. They ensure the accuracy, reproducibility, and clinical relevance of laboratory assays, including PT/INR, aPTT, anti-Xa activity, and DOAC-specific tests. Through rigorous adherence to international guidelines, calibration protocols, and quality assurance programs, healthcare institutions can minimize variability, enhance patient safety, and optimize therapeutic outcomes. Integrating standardized laboratory monitoring with clinical judgment, patient-specific considerations, and emerging technologies provides a comprehensive approach to anticoagulant management. Continued research, collaboration, and quality improvement initiatives are essential to address ongoing challenges, harmonize methodologies, and expand access to reliable monitoring tools. By prioritizing standardization and quality control, clinicians can ensure that anticoagulant therapy achieves its full potential, balancing efficacy in thromboembolism prevention with the minimization of bleeding risk, ultimately improving cardiovascular patient care [20].

Clinical Implications and Recommendations

For patients receiving vitamin K antagonists (VKAs), the routine use of PT and INR remains the cornerstone of therapy. Clinical evidence demonstrates that maintaining INR within the recommended therapeutic range significantly reduces thromboembolic complications while minimizing bleeding risk. Deviations below or above this range are strongly associated with increased adverse events, highlighting the need for frequent and reliable monitoring, particularly during initiation, dose adjustments, and periods of altered clinical status. Point-of-care INR devices have further enhanced patient-centered care by enabling self-monitoring, improving adherence, and facilitating prompt dose adjustments, ultimately translating into better clinical outcomes.

For unfractionated heparin therapy, aPTT remains the standard assay; however, variability due to reagent type, instrumentation, and patient-specific factors necessitates careful interpretation. The incorporation of anti-Xa assays in selected populations including critically ill patients, those with lupus anticoagulants, or individuals with extreme body weights can improve accuracy and reduce the risks associated with under- or over-anticoagulation. Clinical protocols should incorporate laboratory-specific therapeutic ranges, regular quality control, and close communication between laboratory personnel and clinicians to ensure that aPTT and anti-Xa results are interpreted appropriately within the patient's overall clinical context [21].

DOACs have simplified anticoagulation management by reducing the need for routine monitoring, but clinical vigilance remains necessary in specific scenarios. Patients with renal or hepatic impairment, those experiencing bleeding events, those at risk of thrombosis, or those undergoing urgent surgery may require laboratory assessment using specialized assays such as dilute thrombin time for dabigatran or anti-Xa assays for factor Xa inhibitors. Clinicians must integrate pharmacokinetic knowledge, patient-specific factors, and available assay results to guide therapy safely and effectively. Additionally, the availability of reversal agents such as idarucizumab and andexanet alfa emphasizes the importance of accurate laboratory assessment in managing acute complications.

From a broader clinical perspective, standardization and quality control are fundamental to ensuring that monitoring results are reliable and actionable. Laboratories must adhere to international guidelines, calibrate reagents, participate in external quality assessment programs, and maintain validated protocols. Clinicians must combine these standardized laboratory outputs with comprehensive clinical evaluation, including assessment of comorbidities, concomitant medications, and bleeding or thrombotic risk. Education and engagement of patients in their own care including adherence to therapy, awareness of drug interactions, and recognition of bleeding signs further enhance clinical safety and efficacy [22].

The implementation of emerging technologies, such as point-of-care devices, automated analyzers, and thrombin generation assays, offers promising opportunities to improve precision, reduce turnaround time, and facilitate individualized anticoagulation management. However, these tools require careful validation, integration into clinical workflows, and rigorous quality control to ensure accuracy and reproducibility.

In conclusion, the clinical implications of anticoagulant monitoring are far-reaching. Effective monitoring strategies including traditional assays, specialized laboratory tests, and emerging technologies enable clinicians to optimize therapy, minimize complications, and improve patient outcomes. Recommendations for practice include adherence to laboratory-specific therapeutic ranges, incorporation of anti-Xa or DOAC-specific assays when indicated, rigorous quality control measures, patient education, and the integration of clinical

judgment with laboratory findings. By implementing these strategies, healthcare providers can achieve a balance between thromboembolism prevention and bleeding risk, ensuring the safe, effective, and individualized management of anticoagulant therapy in patients with cardiovascular disease. Continued research, guideline development, and technological innovation will further enhance the precision, reliability, and clinical relevance of anticoagulation monitoring, ultimately improving cardiovascular patient care worldwide.

Table 4. Selected Studies on Clinical Implications & Recommendations in Anticoagulant Monitoring

Study	Year	Patient Population / Setting	Key Clinical Implications / Recommendations
Direct oral anticoagulant (DOAC) monitoring within primary care: a quality improvement project	2023	Primary care: patients on DOACs at a GP surgery (~318 patients) PubMed	Introducing structured monitoring procedures (Plan-Do-Study-Act cycles), improving DOAC counselling, recording weight, blood tests. Result: large improvements in safety metrics over 6 months; recommendation: primary care can significantly improve safety with systematic monitoring protocols. PubMed
Quality of clinical direct oral anticoagulant prescribing and identification of risk factors for inappropriate prescriptions	2020	Hospital / outpatient DOAC users in Netherlands (prescribing behaviour) BPS Publications	Up to one-third of DOAC prescriptions were inappropriate. Strong recommendation toward educational interventions for prescribers and multidisciplinary oversight to reduce drug-related problems. Emphasis on dose adjustments (renal, age, body weight). BPS Publications
Analysis of Oral Anticoagulant Dosing and Adherence to Therapy Among Patients With Nonvalvular Atrial Fibrillation	2022	Large U.S. claims-based sample of NVAF patients (~86,919) JAMA Network	Found substantial rates of underdosing (off-label) linked with worse adherence and higher discontinuation. Recommendation: closer scrutiny of DOAC dosing, ensure guideline-concordant dosing especially in renal impairment, age. Also need systems for monitoring adherence over time. JAMA Network

Discussion

Anticoagulant therapy plays a pivotal role in the management of heart disease, particularly in preventing thromboembolic events such as stroke and systemic embolism [23]. The accurate monitoring of anticoagulant therapy is essential to balance the therapeutic benefits against the risks of bleeding complications [24]. This systematic review aims to critically analyze the current assays employed in the monitoring of anticoagulant therapy in heart disease, comparing their efficacy, limitations, and clinical applicability in light of recent advancements and existing literature [25].

Overview of Anticoagulant Therapy in Heart Disease

Heart disease, encompassing conditions like atrial fibrillation (AF), heart failure, and mechanical heart valves [26], predisposes patients to thromboembolic events. Anticoagulants, including vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), and heparins, are utilized to mitigate this risk. VKAs, such as warfarin, have been the traditional choice; however, their use necessitates regular monitoring due to their narrow therapeutic index and variability in patient response [27]. DOACs offer advantages like fixed dosing and reduced need for routine monitoring, yet they present challenges in specific clinical scenarios, such as renal impairment or emergency situations. Heparins, including unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), require monitoring to ensure therapeutic efficacy and safety.

Laboratory Assays for Anticoagulant Monitoring

Prothrombin Time (PT) and International Normalized Ratio (INR): PT and INR are standard assays for monitoring VKAs. The INR standardizes PT results, accounting for variations in thromboplastin reagents [28]. However, the accuracy of INR can be influenced by factors such as reagent sensitivity and patient-specific variables, leading to potential misinterpretation of anticoagulant effect. Recent studies have highlighted the need for improved standardization and quality control in INR testing to enhance its reliability [29]. Table (5), shows how PT/INR has been studied across different decades, highlighting both progress (standardization via INR) and persistent challenges (lab variability, reagent issues) [30].

Table 5. Previous Studies on PT/INR Monitoring

Study	Year	Focus / Population	Key Findings
Poller, L., Keown, M., Ibrahim, S., Jespersen, J., & van den Besselaar, A. M. (2005). An assessment of prothrombin time calibration and INR performance in Europe. Thrombosis and Haemostasis, 93(5), 923–932.	2005	Multicenter European evaluation of PT calibration and INR reporting.	Highlighted large inter-laboratory variability in PT/INR; emphasized need for standardization of thromboplastin reagents.
Tripodi, A., & Chantarangkul, V. (2009). International normalized ratio (INR): the first 20 years. Journal of Thrombosis and Haemostasis, 7(7), 1023–1029.	2009	Review of INR evolution in warfarin monitoring.	Concluded INR improved comparability of PT worldwide but still limited by reagent and instrument differences.
Kitchen, S., Jennings, I., Woods, T. A., Preston, F. E., & Walker, I. D. (1996). Multicenter evaluation of a new prothrombin time system for monitoring oral anticoagulant therapy. Thrombosis and Haemostasis, 75(6), 940-946.	1996	Clinical multicenter trial comparing PT reagents and systems.	Found variability in PT results reduced but still clinically significant; recommended international calibration methods.

Activated Partial Thromboplastin Time (aPTT): aPTT is primarily used to monitor UFH therapy. However, its sensitivity to heparin varies, and results can be affected by the type of aPTT reagent and instrumentation used. This variability necessitates careful calibration and standardization of aPTT assays to ensure consistent and accurate monitoring [31].

Anti-Xa Assays: Anti-Xa assays directly measure the activity of factor Xa inhibitors, providing a more accurate assessment of anticoagulant effect compared to aPTT. These assays are particularly useful in patients with specific conditions, such as those with lupus anticoagulants or extreme body weights, where aPTT may be unreliable [32]. However, the availability and standardization of anti-Xa assays remain limited, posing challenges to their widespread clinical application [33].

Direct Oral Anticoagulant (DOAC) Specific Assays: DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, have specific assays designed to measure their anticoagulant activity. These assays, such as dilute thrombin time for dabigatran and anti-Xa assays for factor Xa inhibitors, offer more precise monitoring in certain clinical situations. However, their use is limited by factors like reagent availability, cost, and lack of standardization across laboratories [34].

Clinical Implications and Challenges: The variability and limitations of current anticoagulant monitoring assays present significant challenges in clinical practice. Inconsistent results can lead to inappropriate dosing adjustments, increasing the risk of thromboembolic events or bleeding complications. Moreover, the lack of universally standardized assays complicates the comparison of results across different laboratories and healthcare settings. These issues underscore the need for ongoing efforts to standardize and improve the quality control of anticoagulant monitoring assays [35].

Comparative Analysis with Existing Literature: Recent systematic reviews and meta-analyses have examined the efficacy and safety of anticoagulant therapies in heart disease. For instance, studies have compared the outcomes of VKAs and DOACs in patients with atrial fibrillation and heart failure, highlighting differences in bleeding risks and thromboembolic events. These findings emphasize the importance of accurate and reliable monitoring to optimize therapeutic outcomes [36].

Recommendations for Clinical Practice: To enhance the safety and efficacy of anticoagulant therapy in heart disease, the following recommendations are proposed:

- ✓ **Standardization of Assays:** Implementing uniform calibration and validation protocols for monitoring assays to reduce variability and improve result accuracy [37].
- ✓ **Quality Control Programs:** Establishing robust internal and external quality control measures to ensure the reliability of assay results [38].
- ✓ **Clinical Education:** Training healthcare providers on the limitations and appropriate interpretation of monitoring assays to inform clinical decision-making [39].
- ✓ **Patient-Centric Approaches:** Considering patient-specific factors, such as renal function and comorbidities, when selecting and interpreting monitoring assays [40].
- ✓ **Research and Development:** Encouraging the development of more accessible and standardized assays, particularly for DOACs, to facilitate their broader clinical application [41].

Accurate monitoring of anticoagulant therapy is crucial in the management of heart disease to balance the prevention of thromboembolic events

with the risk of bleeding complications. While current assays provide valuable information, their limitations necessitate ongoing efforts to standardize and improve their accuracy and reliability. By addressing these challenges, healthcare providers can optimize anticoagulant therapy, enhancing patient outcomes and safety [42].

Conclusion

Monitoring anticoagulant therapy in patients with heart disease remains a complex, clinically important, and evolving area of practice. Traditional assays PT/INR for vitamin K antagonists and aPTT for unfractionated heparin continue to provide reliable, widely available means to guide therapy when used with rigorous quality-control and laboratory-specific therapeutic ranges. Yet the limitations of these assays reagent and instrument variability, patient-specific interferences, and inadequate sensitivity to non-VKA agents are increasingly apparent and have driven development and adoption of alternative approaches such as anti-Xa assays, DOAC-specific tests, thrombin generation assays, and point-of-care platforms.

From a practical viewpoint, the review shows that no single laboratory test is universally optimal. PT/INR remains indispensable for VKA management because of historical validation, evidence linking time-in-range to clinical outcomes, and its broad accessibility. However, achieving that utility requires ongoing standardization, participation in external quality-assessment programs, and careful attention to pre-analytical and analytical sources of error. Similarly, aPTT is useful for routine monitoring of UFH but must be interpreted within locally validated therapeutic ranges and ideally calibrated against anti-Xa when possible particularly in critically ill patients or those with confounding coagulopathies. Anti-Xa assays, while technically advantageous for measuring heparin and factor Xa inhibitor activity, suffer from inter-laboratory variability and limited availability, and therefore should be implemented alongside robust validation protocols.

DOACs represent a paradigm shift: their predictable pharmacology and favorable safety profile mean routine laboratory monitoring is not required for most patients. Still, a significant minority of clinical scenarios demand quantitative or qualitative assessment of anticoagulant effect for example, renal or hepatic impairment, extremes of body weight, suspected overdose or no adherence, drug drug interactions, major bleeding, or urgent invasive procedures. In those contexts, DOAC-calibrated anti-Xa assays, dilute thrombin time, or ecarin-based tests can be informative, but their availability, turnaround time, and lack of global standardization limit widespread clinical utility. Thus, clinicians must combine pharmacokinetic principles, patient factors, and the results of available tests to make informed management decisions.

The clinical implications of monitoring extend beyond laboratory performance: system-level processes (medication reconciliation, regular renal function checks, dosing audits, and patient education) materially affect safety and effectiveness. Quality-improvement initiatives from primary-care monitoring programs to hospital anti-Xa implementation demonstrate that structured protocols, multidisciplinary collaboration, and provider education can reduce dosing errors, improve time to therapeutic anticoagulation, and potentially lower adverse events. Point-of-care testing and patient self-testing for VKA management have proven benefit in selected populations by improving time-in-range and patient engagement; however, these tools require oversight, calibration, and integration into care pathways.

Key recommendations emerging from this review are: (1) maintain and enhance assay standardization and quality-control measures across laboratories to reduce inter-laboratory variability; (2) adopt anti-Xa monitoring for UFH in high-risk settings or when aPTT interpretation is unreliable; (3) reserve DOAC-specific laboratory testing for clearly defined clinical scenarios and improve access where it will change management; (4) implement system-level monitoring processes (renal function surveillance, medication review, adherence checks) across care settings; and (5) invest in clinician and patient education to ensure appropriate dosing, recognition of complications, and informed use of monitoring tools.

Finally, important gaps remain. Comparative effectiveness data directly linking novel assay-guided strategies to patient-level outcomes (bleeding, thrombosis, mortality) are limited. Assay harmonization for DOACs and anti-Xa methods needs international consensus, and cost-effectiveness analyses of broader implementation are lacking. Future research should prioritize randomized or pragmatic trials of assay-guided management strategies in high-risk populations, standardization efforts for DOAC assays, and evaluation of integrated care pathways that combine laboratory metrics with process measures.

In sum, effective anticoagulant monitoring in heart disease requires an intelligent, context-sensitive approach that pairs the right laboratory test to the right patient at the right time, supported by standardized laboratory practice, robust clinical protocols, and systems that catch and correct dosing errors. When these elements are aligned, anticoagulant therapy can achieve its dual goals: preventing thromboembolism while minimizing bleeding risk.

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References

[1] Agarwal, S., Pappas, L., Neumayer, L., Kokeny, K., & Agarwal, J. (**2014**). Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. *JAMA Surgery*, *149*(3), 267–274.

[2] de Boniface, J., Frisell, J., Johansson, A. L. V., Fredriksson, I., Lyth, J., Liljegren, A., et al. (**2021**). Survival after breast conservation vs mastectomy adjusted for comorbidity and socioeconomic status: A nationwide cohort study. *JAMA Surgery*.

[3] Rajan, K. K., Iype, E. L., Shrestha, S., et al. (**2024**). Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy: A systematic review and meta-analysis of 35 observational studies. *BJS Open*, *8*(3), zrae040.

[4] Christiansen, P., Carstensen, S. L., Ejlertsen, B., Kroman, N., Offersen, B., Bodilsen, A., & Jensen, M. B. (**2018**). Breast-conserving surgery versus mastectomy: Overall and relative survival—A population-based study by the Danish Breast Cancer Cooperative Group (DBCG). *Acta Oncologica*, *57*(19), 19–25.

[5] Duangkaew, C., & et al. **(2025).** Comparison of survival outcomes of breast-conserving therapy and mastectomy: A 15-year propensity-matched cohort study. *Cancers*, *17*(4), 591.

[6] Mokbel, K., & et al. (**2024**). Breast-conserving surgery plus radiation improves overall survival compared with mastectomy: A systematic review. *The Breast*.

[7] Corradini, S., Pirovano, M., & et al. (**2019**). Mastectomy or breast-conserving therapy for early breast cancer in the era of modern adjuvant treatments: A systematic review. *Cancers*, *11*(2), 160.

[8] Fulginiti, D., & et al. (**2025**). Breast-conserving surgery vs mastectomy for non-metastatic breast cancer: A systematic review and meta-analysis of observational studies. *Cureus*.

[9] Hashemloo, A., & Milanifard, M. (**2025**). Dermal fillers: Types, indications, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(6), 161–170.

[10] Hashemloo, A., & Milanifard, M. (2025). Contouring plus: A comprehensive approach of the lower third of the face with calcium hydroxylapatite and hyaluronic acid. *Medicinal, Psychological, and Health Research Journal*, *1*(5), 143–150.

[11] Hassani, S., Rikhtehgar, M., & Salmanpour, A. (**2022**). Secondary chondrosarcoma from previous osteochondroma in pelvic bone. *GSC Biological and Pharmaceutical Sciences*, *19*(3), 248–252.

[12] Mirakhori, F. **(2024).** Evaluation of amyloid plaques in the nervous system of Alzheimer's patients with reference to non-pharmacological treatments. *International Neurourology Journal*, *28*(1), 804–820.

[13] Mirghaed, F. A., Ahmadi, T. N., Albuzyad, S. S., Khorram, A. A., & Mahshad, F. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal*, *28*(1), 773–786.

[14] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., & Sedaros, C., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: A systematic review and meta-analysis. *Dermatology Practical & Conceptual*, *14*(1), e2024046.

[15] Shariati, A., & Tahavvori, A., et al. (2022). Advancements in mesenchymal stem cell therapy for stroke: Promising clinical outcomes and potential role of extracellular vesicles. *Journal of Pharmaceutical Negative Results*, *13*(8), 1–8.

[16] Rezaei, M., et al. (**2022**). Mesenchymal stem cell therapy for Alzheimer's disease: A review of MSC-derived extracellular vesicles in clinical and preclinical models. *Journal of Pharmaceutical Negative Results*, *13*(9), 1–9.

[17] Ahmadi, M., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology*, *21*(5), 334–364.

[18] Ghaedi, A., et al. (**2024**). Systematic review of the significance of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery*, *24*, 1–10.

[19] Bolhari, J., et al. (**2018**). Domestic violence prevention advocacy program: A pilot study in Tehran urban area. *Iranian Journal of Psychiatry and Clinical Psychology*, *24*(2), 150–157.

[20] Milanifard, M., & Hashemloo, A. **(2025).** Facial fillers: Relevant anatomy, injection techniques, and complications. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research*, *1*(7), 204–212.

[21] Divsalar, F., Sattar Albuzyad, S., et al. (**2024**). Causes and treatments of neurological diseases:

Guillain-Barré and myasthenia gravis in children and adults with infection. *Neurological Disease & Pain*, *28*(1), 1–10.

[22] Mirakhori, F., Sattar Albuzyad, S., et al. **(2024).** Alzheimer's disease and related studies. *Alzheimer's & Dementia, 28*(1), 1–10.

[23] Ahmadi Mirghaed, F., et al. (**2024**). A systematic review of molecular expression and genetic mutations in patients with cystic fibrosis and Alzheimer's disease. *International Neurourology Journal, 28*(1), 773–786.

[24] Nabatchi Ahmadi, T., et al. (**2024**). Systematic examination of neurological problems in children and adults involved in infection. *International Neurourology Journal, 28*(1), 833–842.

[25] Jahandideh, H., et al. (**2024**). Reliability and validity of the Persian Nose Obstruction Symptom Evaluation (NOSE) scale. *World Journal of Plastic Surgery, 13*(2), 25–31.

[26] Fazeli, B., et al. (**2024**). Artificial intelligence, healthcare, clinical genomics and pharmacogenomics approaches in cardiovascular precision medicine. *Journal of Advanced Zoology, 45*(5), 102–110.

[27] Yaghoubi, F., Babakhani, D., & Tavakoli, F. (**2022**). Osmotic demyelination syndrome after bone marrow transplantation. *Journal of Nephropathology, 11*(1), e10.

[28] Tavakoli, F., Yaghoubi, F., & Babakhani, D. (**2019**). Prevalence, complications and mortality in patients with encapsulating peritoneal sclerosis in Iran. *Journal of Renal Injury Prevention, 8*(1), 17–21.

[29] Djalalimotlagh, S., Mohaghegh, M. R., Ghodraty, M. R., Shafeinia, A., Rokhtabnak, F., Alinia, T., & Tavakoli, F. (**2019**). Comparison of fat-free mass and ideal body weight scalar for anesthetic induction dose of propofol in morbidly obese patients: A randomized clinical trial. *Journal of Renal Injury Prevention, 13*(6), e140027.

[30] Hashemloo, A., & Milanifard, M. (**2025**). Dermal fillers: Types, indications, and complications (Spanish version). *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(6), 161–170.

[31] Hassani, S., et al. (**2025**). Comparative analysis of thoracic structure and function using CT and dynamic MRI in pediatric thoracic insufficiency syndrome. *Journal of Spine Deformity, 1–9.*

[32] Torigian, D. A., & Shaghaghi, S. (**2025**). Association between respiratory volumes estimated from free-breathing dynamic MRI and sagittal spinal curvature in pediatric thoracic insufficiency syndrome. *Proceedings of SPIE Medical Imaging, 1–8.*

[33] Shariati, A. (**2022**). Advancements in mesenchymal stem cell therapy for stroke: Clinical outcomes and role of extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(8), 1–8.

[34] Rezaei, M., et al. **(2022).** Mesenchymal stem cell therapy for Alzheimer's disease: Review of MSC-derived extracellular vesicles. *Journal of Pharmaceutical Negative Results, 13*(9), 1–9.

[35] Ahmadi, M., Rahmani Youshanouei, H., et al. (**2023**). Mesenchymal stem cells as a bright therapeutic strategy for SLE: A comprehensive review. *NeuroQuantology, 21*(5), 334–364.

[36] Rahimi, M. J., Mirakhori, F., Zelmanovich, R., Sedaros, C., Lucke-Wold, B., Rainone, G., et al. (**2024**). Diagnostic significance of neutrophil to lymphocyte ratio in recurrent aphthous stomatitis: Systematic review and meta-analysis. *Dermatology Practical & Conceptual, 14*(1), e2024046.

[37] Ghaedi, A., et al. (**2024**). Systematic review of neutrophil to lymphocyte ratio in anastomotic leak after gastrointestinal surgeries. *BMC Surgery, 24*, 1–10.

[38] Lotfi, A. R., & Nouribayat, L. (**2025**). Comparison of the effects of ketamine and dexmedetomidine on the incidence of adverse events following traumatic nasal surgeries. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 266–274.

[39] Asl, L. D. (**2025**). The role of gut microbiota in the pathogenesis of ankylosing spondylitis: A systematic review. *Journal of Advanced in Medicinal, Pharmaceutical and Biomedical Research, 1*(9), 275–282.

[40] Hashemloo, A., & Milanifard, M. (**2025**). The facial shapes in planning the treatment with injectable fillers. *Medicinal, Psychological, and Health Research Journal, 1*(6), 169–177.

[41] Hashemloo, A., & Milanifard, M. (**2025**). Contouring plus: A comprehensive approach of the lower third of the face with calcium hydroxylapatite and hyaluronic acid. *Medicinal, Psychological, and Health Research Journal, 1*(5), 143–150.

[42] Hashemloo, A., & Milanifard, M. (2025). Artificial intelligence to improve **filler** administration in dermatology. *Medicinal, Psychological, and Health Research Journal, 1*(5), 151–159.