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Review article

Implementing digital twin technology in organ transplantation: Concepts, emerging evidence, and clinical translation pathways

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ABSTRACT

Digital twins are emerging as transformative tools in modern healthcare, representing a paradigm shift toward precision medicine by offering living, data-driven computational replicas of patients or organs that evolve with real-time information. As solutions to the growing demand for personalised, precision-based therapeutic approaches, digital twins play a particularly significant role in transplantation, which is characterised by its data-rich care pathway, time-critical decisions, and complex lifelong immunologic management, making it an ideal environment for precision medicine applications. This narrative review examines how digital twins are being conceptualised and applied across the entire transplant lifecycle, from donor assessment and organ preservation through to operative planning, immunosuppression management, and long-term surveillance, while proposing a pragmatic roadmap for clinical translation. We conducted targeted literature searches between June and October 2025, focusing on digital twin applications in transplantation, machine perfusion technologies, precision immunosuppression dosing, immune modelling, and virtual organ systems. We prioritised scoping reviews, mechanistic studies, clinical investigations, and authoritative technology sources. Foundational applications include liver virtual twins for living donor transplantation, data streams from normothermic machine perfusion platforms enabling organ quality assessment, model-informed precision dosing systems for tacrolimus approaching closed-loop control, and conceptual immune system twins for rejection risk prediction. Evidence ranges from mechanistic simulations and preprints to early clinical pharmacokinetic and pharmacodynamic studies, though rigorous prospective validation remains limited. Digital twins hold substantial promise for augmenting transplant decisions throughout the clinical pathway, but require rigorous validation, interoperable data infrastructure, and governance frameworks aligned with safety and equity principles before widespread adoption.

1. Introduction

The concept of a digital twin, originally developed in manufacturing and aerospace engineering, has recently captured the imagination of the medical community as a powerful tool for personalised healthcare delivery [1,2]. In the era of precision medicine, where treatments are increasingly tailored to individual patient characteristics, digital twins represent a technological solution that enables the shift from population-based to truly individualised care. In the healthcare context, a digital twin represents a dynamic, computational replica of a patient or organ that maintains a bidirectional connection with its physical counterpart, continuously updating as new data becomes available and

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potentially influencing clinical decisions in real time [3–5]. This distinguishes digital twins from static digital models, which lack automatic data exchange, and digital shadows, which passively mirror data streams without closing the control loop [6]. These distinctions carry significant implications for regulatory classification, risk management, and the assessment of clinical maturity in healthcare applications.

Organ transplantation stands out as a particularly compelling domain for digital twin implementation [5,7], serving as a model system for precision medicine where individualised treatment approaches are not merely beneficial but essential for optimal outcomes. The field is characterised by discrete, data-intensive phases spanning the entire care continuum: donor evaluation and organ allocation; ex vivo organ preservation and transport; surgical planning and execution; early post-operative immunosuppression optimisation; and lifelong graft surveillance with ongoing immunologic management [8,9]. Each phase generates substantial volumes of physiologic, biochemical, imaging, and molecular data that could feed sophisticated computational models [10,11]. Moreover, transplantation involves high-stakes, time-sensitive decisions where even marginal improvements in prediction accuracy or dosing precision can translate into meaningful differences in patient outcomes, graft survival, and healthcare resource utilisation [12,13], making it an ideal testbed for precision medicine technologies.

Recent technological advances have converged to make transplant-focused digital twins increasingly feasible. Multi-omics platforms now enable comprehensive profiling of immune responses, graft injury, and drug metabolism at the molecular level [14,15]. Normothermic machine perfusion devices maintain donor organs in a metabolically active state outside the body whilst streaming continuous physiologic parameters [16,17]. Wearable sensors and point-of-care diagnostic devices promise high-frequency monitoring of immunosuppressant levels and biomarkers in ambulatory settings [18,19]. Artificial intelligence and machine learning algorithms have demonstrated remarkable capabilities for integrating heterogeneous data sources and generating actionable predictions [20,21]. The confluence of these developments creates an unprecedented opportunity to realise the digital twin vision in transplantation.

Despite this promise, the field remains in the early stages of development, though it is advancing rapidly. Most systems described as digital twins in transplantation are more accurately classified as digital models or shadows, lacking the bidirectional integration and adaptive control that define true twinning [6,22], with recent comprehensive reviews confirming that very few healthcare implementations meet full digital twin criteria [4,23,24]. The evidence base consists primarily of mechanistic simulations, retrospective analyses, industry-reported capabilities, and small pilot studies, with few prospective clinical trials demonstrating improved patient outcomes [25,26], though the number of proof-of-concept studies is growing substantially [20]. Significant challenges remain in data interoperability, model validation across diverse populations, regulatory pathways, ethical governance, and the practical integration of digital twins into existing clinical workflows [1,3,27], particularly regarding real-time data connectivity and adaptive control mechanisms [23]. Addressing these gaps requires a systematic understanding of current capabilities, explicit recognition of limitations, and a pragmatic roadmap for progressive implementation.

The problem this review addresses is the need for a comprehensive synthesis of digital twin applications across the transplant lifecycle, clarifying the current state of evidence, identifying the most promising near-term opportunities, and articulating the technical, clinical, regulatory, and ethical prerequisites for successful translation. The rationale lies in transplantation's unique position as a data-rich, decision-intensive field where computational tools could deliver outsized benefits if properly developed and validated. The novelty of our approach lies in integrating perspectives spanning organ-specific virtual twins, machine perfusion technologies, precision pharmacology, immune modelling, and enabling platforms within a unified conceptual framework and a staged implementation roadmap. We aim to narratively review the conceptualisation and application of digital twins throughout transplantation and propose a pragmatic translation pathway. Our objectives are to define digital twin taxonomy relevant to transplantation, survey emerging applications across the donor to recipient care continuum, examine enabling technologies and data infrastructure, assess the current evidence landscape and maturity, consider ethical and regulatory dimensions, and outline a phased roadmap prioritising high-value use cases whilst building toward more sophisticated implementations.

2. Methods

This narrative review employed a targeted, non-systematic search strategy designed to capture representative and load-bearing literature on digital twins in transplantation and related domains. Between June and October 2025, we conducted searches in PubMed, Google Scholar, and preprint servers including bioRxiv and medRxiv, using combinations of key terms: “digital twin,” “transplantation,” “organ transplant,” “machine perfusion,” “normothermic perfusion,” “tacrolimus,” “immunosuppression dosing,” “model informed precision dosing,” “immune digital twin,” “liver virtual twin,” “organ on chip,” and “multi omics.” We prioritised scoping reviews, mechanistic and clinical studies, authoritative technology sources, professional society statements, and industry white papers that illustrated current capabilities and implementation examples.

We supplemented database searches with forward and backward citation tracking of seminal papers, a review of transplant society conference abstracts featuring digital twin concepts, and an examination of device manufacturer documentation for machine perfusion platforms. Grey literature, including regulatory guidance documents and health technology assessment reports, was consulted to understand governance considerations. Given the nascent and rapidly evolving nature of this field, we intentionally included preprints and early-stage work alongside peer-reviewed publications to capture the frontier of development.

Inclusion criteria encompassed any source describing conceptual frameworks, technical implementations, or clinical applications of digital twins or closely related computational tools in solid organ transplantation, with particular attention to liver, kidney, heart, and lung transplantation. We also included foundational work on digital twin taxonomy in healthcare, precision dosing platforms, multi-omics integration, and organ-on-chip systems, all of which had clear relevance to transplant applications. Exclusion criteria were non-English-language publications, purely theoretical expositions without a connection to transplant biology or clinical care, and studies focused exclusively on digital health interventions without twin-like features.

Data extraction focused on identifying the phase of transplant care addressed, the type of digital twin or related system, the data sources and computational methods employed, the level of clinical validation, and any reported outcomes or performance metrics. We synthesised findings narratively, organising content by stage of the transplant lifecycle and cross-cutting themes such as enabling technologies and implementation barriers. Three summary tables were constructed to present the digital twin taxonomy, applications across the transplant pathway, and a staged implementation roadmap without duplicating narrative content.

3. Digital twin taxonomy in transplantation

Understanding what qualifies as a digital twin in the healthcare context is essential for assessing maturity, managing expectations, and establishing appropriate regulatory frameworks. The term has been applied loosely to a wide range of computational tools, creating confusion about capabilities and requirements [22]. A practical taxonomy distinguishes three categories based on the nature of data connectivity and control.

Digital models represent the most basic category: computational representations of anatomy, physiology, or pharmacology that do not automatically exchange data with the physical entity [28,29]. In transplantation, examples include static three-dimensional reconstructions of liver anatomy derived from preoperative computed tomography scans used for surgical planning. These models are built once from a snapshot of data and do not update as the patient's condition evolves [30,31]. Whilst valuable for visualisation and rehearsal, they lack the dynamic, responsive character that defines twinning [30]. Their utility is time-limited, and they require manual updating if circumstances change. Nevertheless, digital models serve as foundational stepping stones, establishing workflows for image processing, model generation, and integration into clinical decision-making [20,21].

Digital shadows introduce one-way connectivity: they continuously or periodically ingest data streams from devices, electronic health records, or sensors, mirroring the state of the physical system in real time or near-real time [6,32]. In transplantation, a prototypical digital shadow would be a dashboard displaying live perfusion parameters during normothermic machine perfusion of a donor organ, including flow rates, vascular resistance, lactate clearance, and pH trends [16,17,33]. The shadow reflects what is happening but does not influence perfusion settings or clinical actions in a closed-loop manner.

Digital twins complete the cycle with bidirectional connectivity and adaptive control. A true twin not only ingests data and updates its internal representation but also generates predictions, simulates counterfactual scenarios, and can recommend or implement interventions that affect the physical counterpart, subject to appropriate oversight [34]. In an idealised transplant digital twin, immunosuppressant drug levels would be measured continuously or at high frequency, feeding a pharmacokinetic and pharmacodynamic model that predicts future drug exposure and rejection risk under various dosing scenarios [35,36]. The twin would then suggest dose adjustments, which, after clinician review and approval, would be implemented, creating a closed loop [23]. The twin learns and adapts as more data accrue, refining its predictions and recommendations to the individual patient's biology [2,5]. This level of integration and autonomy distinguishes twins from shadows and represents the aspirational endpoint of development efforts.

Healthcare-wide scoping analyses emphasise that very few systems operating today meet the full criteria for digital twins. Most implementations fall into the model or shadow categories and are progressing along a maturity continuum toward true twinning [22]. This gradual evolution is appropriate given the stakes involved in medical decision-making and the need for extensive validation before ceding significant autonomy to computational systems. Recognising where current transplant applications sit on this spectrum clarifies realistic expectations and guides prioritisation of next steps. Table 1 summarises this taxonomy with transplant-relevant examples and key characteristics.

4. Applications across the transplant lifecycle

4.1. Pre-transplant evaluation and matching

The pre-transplant phase involves assessing potential recipients' suitability for transplantation, evaluating immunologic risk, and matching available donor organs to recipients on waiting lists [12,37]. Digital twins could enhance multiple facets of this process. Immune digital twins represent one of the most ambitious applications, aiming to create mechanistic and artificial intelligence hybrid models of the human immune system that simulate response trajectories to foreign antigens [38,39]. Such systems would integrate human leukocyte antigen typing, donor-specific antibody profiles, recipient immune status, cytokine signatures, and T cell receptor repertoires to forecast the likelihood of hyperacute, acute, or chronic rejection under different immunosuppression regimens [38,40]. Whilst largely conceptual at present, community initiatives are developing frameworks for immune system modelling that could eventually support twin-like applications in transplantation.

Multi-omics-enabled risk stratification offers a complementary pathway. Advances in genomics, transcriptomics, proteomics, and metabolomics have identified biomarker signatures associated with allograft dysfunction, rejection phenotypes, and tolerance states [41–43]. Integrating these molecular profiles with clinical variables into predictive models creates a foundation for pre-transplant twins that could simulate outcomes across various donor-recipient pairings or immunosuppression strategies [44,45]. For instance, gene-expression panels can distinguish T-cell-mediated rejection from antibody-mediated rejection and predict therapeutic response [46,47]. As these omics platforms become more accessible and affordable, incorporating them into digital twins will enhance fidelity and enable personalised risk assessment that goes beyond conventional scoring systems.

A practical near-term application involves optimising organ allocation decisions. When an organ becomes available, transplant centres must rapidly assess its suitability for a specific recipient, weighing factors including donor quality metrics, cold ischaemia time, recipient acuity, and immunologic compatibility [12]. A digital shadow or early-stage twin that integrates these variables with recipient-specific physiologic and molecular data could generate probabilistic forecasts of graft survival, rejection risk, and patient survival, supporting more informed acceptance decisions [4,48]. Such systems would need rigorous validation against historical outcomes and careful attention to equity, ensuring that algorithmic recommendations do not inadvertently disadvantage marginalised groups.

4.2. Donor organ assessment and preservation

Once an organ is recovered, assessing its quality and maintaining viability during transport to the recipient are critical. Normothermic machine perfusion has revolutionised this phase by keeping organs metabolically active ex vivo, in contrast to traditional cold static storage [49,50]. Devices such as the TransMedics Organ Care System perfuse hearts, lungs, and other organs at physiologic temperatures whilst continuously monitoring flow rates, pressures, oxygen consumption, lactate production, and other parameters [51,52]. These data streams represent prime inputs for digital shadows and emerging twins focused on organ quality assessment.

A real-time organ quality shadow would ingest perfusion telemetry, calculate derived metrics such as hepatic artery flow indices or lactate clearance rates, and compare these against validated thresholds or predictive models to estimate post-implantation function [16,33]. For example, elevated lactate or reduced bile production during liver perfusion correlates with an increased risk of early allograft dysfunction [53]. A more sophisticated organ-quality twin would go further by

Table 1
Digital Twin Taxonomy in Transplantation.

Category	Data Connectivity	Control Loop	Transplant Examples	Maturity Level
Digital Model [20,30]	None (static snapshot)	Open loop, manual use	CT-based liver anatomical models for surgical planning	Foundation
Digital Shadow [16,32]	One way (device/EHR to model)	Open loop, monitoring, and alerts	Normothermic perfusion parameter dashboards; EHR-based graft function tracking	Intermediate
Digital Twin [4,5]	Bidirectional (data in, actions out)	Closed loop with human oversight	Adaptive tacrolimus dosing systems; predictive organ quality twins guiding acceptance	Advanced (aspirational)

simulating counterfactual perfusion strategies, such as altered flow rates, temperature adjustments, or pharmacologic interventions, to improve graft function [40,54]. By testing these scenarios in silico, the twin could guide real-time perfusion optimisation and support go/no-go decisions regarding organ utilisation.

The technical architecture for such twins is increasingly feasible. Perfusion platforms already generate high-resolution time series data, and machine learning algorithms can model complex relationships between perfusion parameters and post-transplant outcomes [10,16]. The translational gap lies in prospective validation: demonstrating that twin-guided decisions improve organ utilisation rates, reduce discard of viable organs, and enhance graft survival compared to current practice. Industry partnerships between device manufacturers and transplant centres are beginning to explore these possibilities, though rigorous, peer-reviewed outcome data remain limited.

4.3. Operative planning and donor recipient surgery twins

Surgical complexity in transplantation, particularly for liver and multivisceral procedures, creates opportunities for digital twins that support operative planning and intraoperative decision making. Liver-specific applications have progressed furthest. Living donor liver transplantation requires careful assessment of donor anatomy and predicted remnant liver volume to ensure donor safety whilst providing adequate graft size for the recipient [12,55]. Mechanistic models of liver regeneration, which simulate hepatocyte proliferation and volumetric recovery following partial hepatectomy, are being integrated with patient-specific clinical and molecular data to create donor-specific liver digital twins [56].

One notable example combines computed tomography imaging, clinical variables, and gene expression profiles to predict post-donation liver regeneration trajectories in living donors [56]. This twin approach supports preoperative counselling about donor risks and informs decisions about which lobe to harvest. By simulating regeneration under different surgical plans, surgeons can optimise graft sizing whilst maintaining donor safety margins [57]. Similar frameworks extend to recipients, where virtual hepatic lobule models simulate microcirculatory dynamics and metabolic function, providing mechanistic insights into early graft function and potential complications.

Professional societies have highlighted emerging liver digital twin applications for surgical navigation and transplant planning, noting their potential to reduce operative times, minimise blood loss, and improve anatomic precision [57–59]. These systems integrate preoperative imaging with intraoperative guidance, overlaying virtual anatomy onto the surgical field [58,59]. Whilst not yet true twins in the sense of closed-loop control, they represent digital shadows with significant clinical utility and are evolving toward greater interactivity as augmented reality and robotics platforms mature [5,22].

Beyond the liver, similar concepts apply to kidney transplantation, where three-dimensional vascular reconstructions guide anastomotic planning [60], and to heart transplantation, where simulations of post-implantation haemodynamic changes inform intraoperative management [61]. The common thread is leveraging computational models to rehearse procedures, anticipate challenges, and personalise surgical strategy to individual patient anatomy and physiology.

4.4. Early post-transplant immunosuppression twins

Immediately following transplantation, patients require intensive immunosuppression to prevent rejection whilst avoiding toxicity from overexposure to calcineurin inhibitors, antiproliferative agents, and corticosteroids [62,63]. Tacrolimus, the mainstay calcineurin inhibitor, exemplifies the challenges and opportunities for digital twin applications in this domain [26]. Tacrolimus exhibits narrow therapeutic windows, substantial inter-individual and intra-individual pharmacokinetic variability driven by genetic polymorphisms in metabolic enzymes (particularly CYP3A5), drug interactions, and changing physiology post-transplant [4,64]. Traditional dosing relies on population averages and therapeutic drug monitoring, often resulting in subtherapeutic or supratherapeutic levels during the critical early period [65].

Model-informed precision dosing represents a major step toward immunosuppression twins. These systems use Bayesian pharmacokinetic models that incorporate patient characteristics, such as weight, age, genotype, and early drug-level measurements, to predict individual tacrolimus exposure and to simulate counterfactual dosing regimens [36,66]. Multiple studies have demonstrated that model-informed approaches achieve target therapeutic ranges faster and maintain time in range more consistently than standard dosing, reducing both rejection episodes and drug-related toxicities [36,67,68]. Machine learning algorithms further enhance these models by capturing nonlinear relationships and incorporating additional covariates such as serum creatinine, albumin, and haematocrit [69,70].

The transition from model-informed dosing tools to true twins requires high-frequency drug monitoring and closed-loop control. Ambient or at-home therapeutic drug monitoring technologies, including saliva-based and micro-sampling devices, promise to provide the dense temporal data that twins need [71]. If patients could measure tacrolimus levels daily or even more frequently, a twin could continuously update its pharmacokinetic estimate, detect deviations from target exposure, and automatically adjust doses under clinician oversight [4,72]. This would represent a genuine closed-loop system, adaptively personalising immunosuppression in real time.

Practical implementation faces hurdles, including regulatory approval for autonomous dose adjustment, ensuring explainability and auditability of recommendations, managing alerts and overrides without creating alarm fatigue, and validating safety across diverse populations [5,38]. Nevertheless, the building blocks are in place: validated pharmacokinetic models, genotyping infrastructure, emerging point-of-care monitoring, and electronic prescribing systems capable of receiving algorithmic inputs [1,66]. Immunosuppression twins thus appear poised to move from concept to reality within the next few years, offering a tractable near-term goal for transplant digital twin implementation [2]. Table 2 summarises applications across the transplant lifecycle, indicating current maturity and key data sources.

4.5. Long-term surveillance for rejection, infection, and adherence

Beyond the early post-transplant period, recipients require lifelong monitoring for chronic rejection, opportunistic infections, malignancy, and metabolic complications of immunosuppression. Adherence to medication regimens is a pervasive challenge, with nonadherence contributing substantially to late graft loss [73]. Digital twins for long term surveillance would integrate diverse data streams, including periodic laboratory tests (creatinine, liver enzymes, viral loads), protocolised and for-cause graft biopsies, wearable sensor data capturing physical activity and vital signs, medication adherence tracking from smart pill bottles or pharmacy refill records, and serial multi omics profiling to detect subclinical rejection or tolerance [14,15,23,26,74].

Immune and inter-organ communication twins represent an aspirational architecture for long-term care [38]. These systems aim to simulate the interplay between graft, host immune system, and other organs, modelling how changes in immunosuppression affect rejection risk, infection susceptibility, renal function, cardiovascular risk, and metabolic control [75,76]. For instance, reducing tacrolimus exposure might lower nephrotoxicity but increase rejection risk [36]; the twin would forecast these trade-offs quantitatively, supporting shared decision-making between clinician and patient about optimal immunosuppression intensity over time.

Chronic rejection, particularly antibody-mediated rejection in kidney transplantation, develops insidiously over months to years. Early detection through surveillance biopsies or non-invasive biomarkers could enable intervention before irreversible damage occurs [77,78]. A

Table 2
Digital Twin applications across the transplant lifecycle.

Transplant Phase	Digital Twin Application	Primary Data Sources	Current Maturity	Potential Impact
Pre-transplant evaluation [38,41]	Immune digital twin for rejection risk	HLA typing, DSA, multi omics, immune repertoires	Conceptual to early prototype	Personalised immunosuppression planning
Organ preservation [17,33]	Organ quality twin from machine perfusion	Flow, pressure, lactate, pH, oxygenation, bile output	Digital shadow to early twin	Optimised organ utilisation, reduced discard
Operative planning [47,56]	Liver virtual twin for donor assessment	CT imaging, gene expression, clinical variables	Pilot studies, preprints	Safer living donation, optimised graft sizing
Early immunosuppression [36,64]	Tacrolimus dosing twin	TDM, genotype, demographics, labs, drug interactions	Model informed dosing validated; closed loop emerging	Faster time in range, reduced rejection and toxicity
Long-term surveillance [15,42]	Whole patient immune and graft function twin	Multi omics, continuous biomarkers, adherence data	Conceptual framework	Proactive rejection prevention, adherence support

surveillance twin would integrate historical biopsy findings, trending donor-specific antibody levels, gene-expression signatures from peripheral blood, and eGFR trajectories to probabilistically forecast rejection episodes and suggest optimal biopsy timing [2,79]. Similarly, infection risk models could incorporate immunosuppression levels, white blood cell counts, prior infection history, and pathogen exposure to guide prophylaxis decisions and alert clinicians to emerging threats [38,80].

Adherence twins address the behavioural dimension of long-term care [81]. By monitoring medication-taking patterns, correlating adherence lapses with drug-level variability or clinical events, and incorporating patient-reported outcomes on barriers to adherence, these systems could trigger personalised interventions such as educational outreach, prescription simplification, or intensified monitoring [1,14,73]. The goal is not surveillance for its own sake but supportive, patient-centred optimisation of lifelong care.

Whilst these long-term surveillance twins remain largely conceptual, the technological components are maturing. Wearable devices and remote monitoring platforms are proliferating; electronic health records increasingly support data extraction and analytical workflows; and multi-omics costs continue to decline [3,19]. The challenge lies in integrating these heterogeneous data types [82,83], validating predictive models for low-frequency but high-stakes outcomes, and designing user interfaces that present actionable insights without overwhelming patients or clinicians. As summarised across the transplant pathway in Fig. 1, digital twins progress from conceptual immune models in pre-transplant evaluation to validated model-informed dosing in early immunosuppression, with varying maturity levels.

5. Enabling technologies and data infrastructure

Realising transplant digital twins depends on several foundational technologies and infrastructure elements that extend beyond algorithmic sophistication. A critical enabler of digital twin functionality is artificial intelligence (AI) and machine learning (ML), which provide the computational capabilities necessary to process complex, multimodal data streams and generate actionable predictions in transplantation contexts. Microphysiological systems, commonly known as organ-on-a-chip platforms, offer one promising avenue [84]. These microfluidic devices recapitulate key aspects of organ physiology in vitro, including perfusion, cellular architecture, and biochemical gradients [84,85]. When coupled with digital twin simulations, microphysiological systems enable calibration of model parameters using experimental data from patient-derived cells or tissue [23]. For instance, hepatocytes from a donor liver biopsy could be cultured in a liver-on-a-chip device, with measured drug metabolism rates informing pharmacokinetic parameters in a personalised dosing twin [86,87]. Whilst still largely research tools, microphysiological systems illustrate how in vitro experimentation and in silico modelling can synergise.

Multi-omics integration frameworks provide another critical enabler. Single-omics analyses (genomics, transcriptomics, proteomics, metabolomics, or immunomics) alone offer a limited perspective; integrative analyses across modalities reveal systems-level understanding of graft biology and host response [15,88]. Machine learning techniques such as multi-view learning, network analysis, and deep learning on multi-omics tensors are maturing rapidly [89]. In transplantation, integrating genetic risk scores, gene expression rejection signatures, proteomic biomarkers of injury, and metabolomic profiles of drug

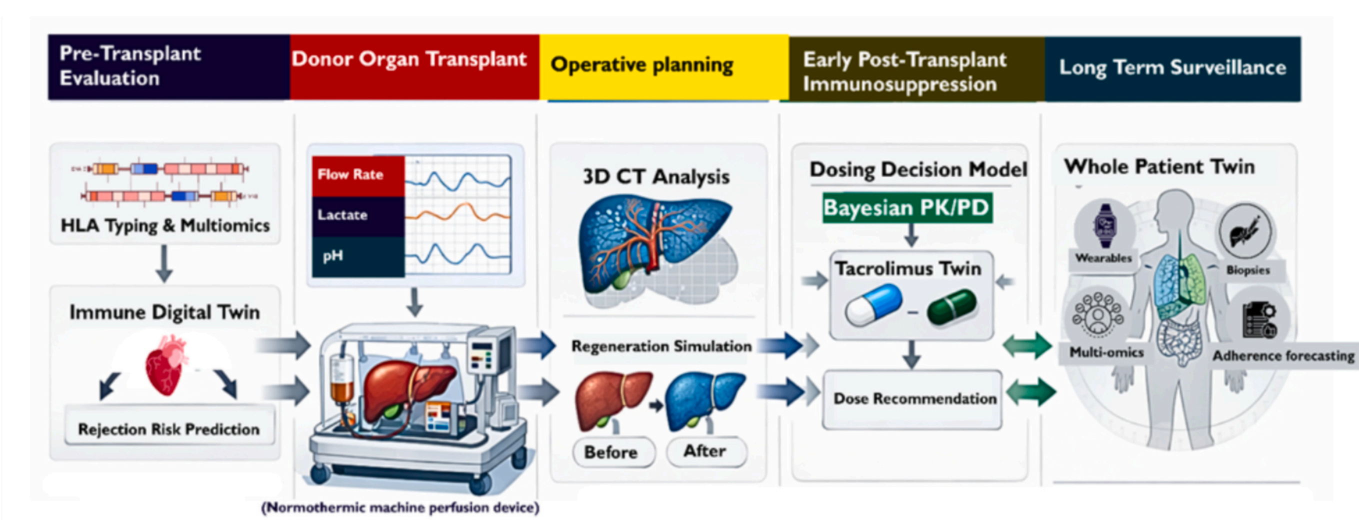

Fig. 1. Digital twin applications across the organ transplantation lifecycle. This schematic illustrates representative implementations at each stage, from pre-transplant immune risk prediction to long-term graft surveillance, highlighting data connectivity, current maturity levels, and potential clinical impacts as synthesised from the reviewed evidence.

exposure could substantially enhance twin fidelity, capturing the complexity of allograft outcomes more faithfully than any single data type [90,91].

Interoperability is perhaps the most pragmatic yet challenging enabler. Digital twins require seamless data flow from electronic health records, laboratory information systems, perfusion device outputs, wearable sensors, patient-reported outcome platforms, and imaging archives [4,26,74]. Achieving this necessitates the adoption of data standards such as Fast Healthcare Interoperability Resources (FHIR), application programming interfaces for device telemetry, and secure cloud infrastructure for data aggregation and computation [92,93]. Without robust interoperability, twins cannot access the diverse, real-time data streams on which their utility depends, and implementations stall at pilot scale within single institutions [94,95]. Health systems and device manufacturers must collaborate on open standards and data-sharing agreements to enable scalable twinning.

Computational infrastructure itself is increasingly accessible. Cloud platforms offer elastic compute resources for training machine learning models and running complex simulations [96]. Edge computing allows some processing to occur locally on perfusion devices or at the bedside, reducing latency for time-critical decisions [97,98]. Secure enclaves and federated learning architectures enable multi-centre model development without centralising sensitive patient data, addressing privacy concerns whilst building generalisable twins [99,100]. These technical solutions are well established in other industries and are being adapted for healthcare.

Finally, human-centred design is essential. Clinicians and patients must find digital twin interfaces intuitive, trustworthy, and aligned with workflows. Explainability tools that articulate why a twin recommends a particular dose or flags a risk are critical for clinical adoption [101,102]. Patient-facing dashboards should present information in lay terms to support engagement and shared decision-making without inducing anxiety [103]. Usability testing, co-design with end users, and iterative refinement based on real-world feedback are prerequisites for translating even the most sophisticated twins into routine practice [14,23].

6. Artificial intelligence and machine learning in transplant digital twins

The integration of artificial intelligence (AI) and machine learning (ML) into digital twin architectures represents a fundamental enabling technology that transforms static computational models into adaptive, predictive systems capable of supporting precision medicine in transplantation. AI and ML algorithms serve multiple critical functions within digital twin ecosystems, including pattern recognition in high-dimensional data, predictive modelling of clinical outcomes, optimisation of therapeutic interventions, and continuous model refinement through learning from new data [20,21].

Current AI applications span several critical domains. In organ quality assessment during machine perfusion, supervised learning algorithms and deep learning models, particularly recurrent neural networks and long short-term memory architectures, analyse continuous streams of perfusion parameters to predict post-transplant graft function with greater accuracy than traditional threshold-based approaches [10,16]. In precision immunosuppression, machine learning algorithms incorporate genetic polymorphisms, drug-drug interactions, organ function parameters, and demographic variables to predict individual dose requirements with higher precision than population-based models, while reinforcement learning approaches show promise for developing adaptive dosing strategies that optimise long-term outcomes [35,69,70]. For multi-omics data integration, deep learning architectures including multi-modal neural networks and graph-based learning algorithms integrate genomic, transcriptomic, proteomic, metabolomic, and immunomic datasets to identify rejection signatures, predict graft survival, and stratify risk [15,21]. Natural language processing and computer vision tools further augment digital twins by extracting structured information from clinical notes, pathology reports, and histopathologic images [20,21].

Future applications include generative AI models for creating synthetic patient cohorts and counterfactual scenario exploration, federated learning architectures enabling multi-center model development without centralising sensitive patient data, and explainable AI (XAI) techniques such as SHAP values and attention mechanisms that illuminate which features drive predictions, maintaining clinical trust and enabling error detection [100,102,104]. AI-powered predictive surveillance capabilities using anomaly detection and time-series forecasting could enable proactive interventions before complications become clinically apparent [79,80].

Significant challenges must be addressed, including data quality issues, algorithmic bias that may exacerbate disparities in transplant outcomes for underrepresented populations, and model drift requiring continuous monitoring and retraining [20,23,105]. Regulatory frameworks for adaptive algorithms that learn from real-world data are evolving, requiring demonstration of safety, effectiveness, and fairness through rigorous validation and ongoing surveillance [5,106,107]. The integration of AI into transplant digital twins represents not a replacement for clinical expertise but an augmentation that enhances human decision-making, positioning AI as increasingly central to realising the precision medicine promise of digital twins in transplantation [10,21].

7. Evidence landscape and maturity assessment

Assessing the current evidence base for transplant digital twins requires distinguishing levels of validation and acknowledging the heterogeneity of claims. The most mature strand is model-informed precision dosing for tacrolimus and other immunosuppressants [72]. Multiple prospective cohort studies and randomised controlled trials have demonstrated that Bayesian pharmacokinetic modelling, often incorporating CYP3A5 genotype, achieves target drug levels more rapidly and maintains therapeutic exposure more consistently than traditional dosing [64,66]. These studies show measurable clinical benefits, including reduced acute rejection rates and lower incidence of nephrotoxicity, though long-term graft survival benefits require larger datasets and longer follow-up [36,66]. Nonetheless, this body of work provides strong evidence that pharmacokinetic twins, even without full closed-loop autonomy, improve early post-transplant outcomes.

Liver virtual twins for living donor transplantation and surgical planning represent another area with emerging evidence. Several groups have published mechanistic models of liver regeneration and volumetric recovery following partial hepatectomy, validating predictions against postoperative imaging in living donors [56,57]. However, prospective multi-centre validation and demonstration of impact on donor safety or surgical decision-making have not yet been reported. The work remains at the proof-of-concept stage, requiring replication across diverse populations and centres before clinical adoption can be recommended.

Organ quality assessment during machine perfusion is supported by observational studies correlating perfusion parameters with post-transplant outcomes [16,54]. For example, lactate clearance during normothermic liver perfusion predicts primary non-function and early allograft dysfunction [33,53,108]. These associations provide the empirical foundation for organ quality shadows and twins [109]. However, no randomised trials have yet compared twin-guided organ acceptance decisions with standard evaluation, and it remains uncertain whether computational tools would improve organ utilisation or graft survival beyond expert clinical judgement [23]. The evidence is sufficient to justify pilot implementations and rigorous evaluation, but not yet definitive.

Immune digital twins and long-term surveillance systems are in earlier stages. Most work consists of mechanistic simulations, computational frameworks, and retrospective analyses identifying predictive biomarkers [38,39]. Whilst these lay the necessary groundwork, prospective validation demonstrating that twin-guided interventions improve clinical outcomes is lacking. The complexity of immune dynamics, the long-term horizons over which chronic rejection develops, and the multifactorial nature of graft survival pose substantial challenges for validation studies.

A scoping review of digital twins across healthcare emphasises that few implementations meet the criteria for true twins with bidirectional control; most are digital models or shadows [22]. For transplantation specifically, the gap between aspirational descriptions and validated, clinically deployed systems is wide. This does not diminish the promise of the field but underscores the need for realistic expectations, explicit acknowledgement of uncertainty, and commitment to rigorous evaluation. Table 3 outlines a staged roadmap for progressive implementation, prioritising evidence generation at each phase. Despite promising applications, significant risks, including algorithmic bias, validation deficits, and regulatory hurdles, must be addressed (Fig. 2).

8. Ethical, regulatory, and operational considerations]

Deploying digital twins in transplantation raises ethical and regulatory questions that extend beyond technical performance [115,116]. Explainability and accountability are paramount. When a twin recommends a specific tacrolimus dose or suggests declining a donor organ, clinicians and patients need to understand the rationale [72,117]. Black box models that provide recommendations without interpretable justification erode trust and hinder error detection [118,119]. Methods for explaining predictions, such as feature importance visualisations or counterfactual analyses, should be integrated into twin interfaces [104]. Audit trails documenting model inputs, outputs, and clinician overrides are essential for pharmacovigilance and continuous quality improvement [120,121].

Data governance encompasses consent, privacy, security, and ownership [122]. Patients must understand what data their twin will use, how it will be stored and protected, and who can access it. Consent processes should be transparent, with options to opt out or limit data sharing whilst still receiving standard care [3,4]. Transplant programmes often span multiple institutions (donor hospitals, transplant centres, long-term care providers), requiring data-sharing agreements and harmonised governance. Regulatory frameworks such as the General Data Protection Regulation in Europe and the Health Insurance Portability and Accountability Act in the United States set baselines [123,124], but transplant twins will push boundaries around automated decision-making and cross-border data flows.

Equity is a critical concern. Digital twins will amplify existing biases if training data overrepresents certain demographic groups or if algorithms optimise for populations that are easier to model [22,23]. Transplantation already faces documented disparities in access, wait times, and outcomes by race, ethnicity, socioeconomic status, and geography [105,125]. Twins that perform poorly for underrepresented groups could exacerbate these inequities [23]. Rigorous fairness audits, stratified performance reporting, and inclusive model development processes are essential. This includes ensuring training datasets reflect population diversity, testing twins across subgroups, and incorporating equity as an explicit objective alongside accuracy and efficiency [105,126].

Human-in-the-loop control recognises that full autonomy is inappropriate for high-stakes medical decisions [127]. Even advanced twins should operate under supervisory control, with clinicians retaining authority to override recommendations and intervene if model behaviour appears erroneous [128]. Guardrails such as dose change limits, mandatory review intervals, and safety stops protect patients during the learning curve [129]. Graduated autonomy models, where twins earn greater independence as evidence accumulates, balance innovation with caution.

Regulatory pathways for digital twins are evolving. Traditional medical device regulations were designed for static software and hardware, not systems that learn and adapt over time [130]. Regulatory agencies, including the United States Food and Drug Administration and the European Medicines Agency, are developing frameworks for adaptive algorithms and software as a medical device, emphasising risk-proportionate oversight, pre-market validation, and post-market surveillance [106,107]. Transplant twins that influence medication dosing or organ acceptance would likely be classified as higher-risk devices requiring clinical trial evidence before approval and ongoing performance monitoring after deployment [5,107].

Operational integration into clinical workflows determines whether twins are actually used. Clinicians already face information overload and alert fatigue; adding another system that generates recommendations must be done thoughtfully [131,132]. Twins should integrate into existing electronic health record platforms, present information concisely, and align with clinical workflows rather than disrupt them [14,26]. Training and change management are necessary to develop users' competence and confidence. Finally, business models and reimbursement structures must support twin implementation [1,133]; without appropriate compensation for the infrastructure and expertise required, adoption will lag regardless of clinical benefit.

9. Limitations of the review

This narrative review has several important limitations that should inform the interpretation of findings. First, our search strategy was targeted rather than systematic and exhaustive. We prioritised breadth across the transplant lifecycle and depth in areas with more mature evidence, but we may have missed relevant publications, particularly in languages other than English or in specialised journals outside our

Table 3
Staged roadmap for progressive implementation of Digital Twin in Transplantation.

Implementation Stage	Recommended Actions	Evidence Requirements	Governance and Safety	Success Metrics
Stage 1: Digital Shadows [32,66,110,111]	Deploy organ quality dashboards from machine perfusion; implement model-informed tacrolimus dosing with human approval	Retrospective validation; observational cohorts showing parameter outcome correlations	Human in the loop for all decisions; alerts and thresholds pre-specified; safety monitoring	Time to therapeutic drug range; organ utilisation rate; clinician satisfaction
Stage 2: Adaptive Dosing Twins [112–114]	Add high-frequency TDM; enable dose auto-suggestion with rapid clinician review; link biomarkers to rejection forecasts	Prospective studies showing improved time in range; non-inferiority or superiority trials vs standard care	Mandatory override capability; audit logs; pharmacovigilance integration; staged rollout by centre	Rejection rate; toxicity events; graft survival at 1 year; equity analysis by subgroup
Stage 3: Mechanistic Twins [23,85]	Integrate organ-specific models calibrated to patient physiology; use MPS data where feasible; simulate surgical plans	Multi-centre validation; outcome trials demonstrating benefit; in silico trial feasibility studies	Model drift detection; update schedules; transparent documentation; ethics review for autonomous functions	Donor safety in living donation; surgical complication rate; long-term graft function; cost effectiveness
Stage 4: Whole Patient Twins [2,5,75]	Deploy immune and inter-organ communication models; adaptive long-term surveillance; adherence and patient engagement loops	Platform trials with synthetic or twin augmented controls; long-term registry data; fairness and equity audits	Continuous post-market surveillance; federated learning for model updates; patient consent and data governance	Late graft loss; patient quality of life; adherence rates; healthcare equity metrics

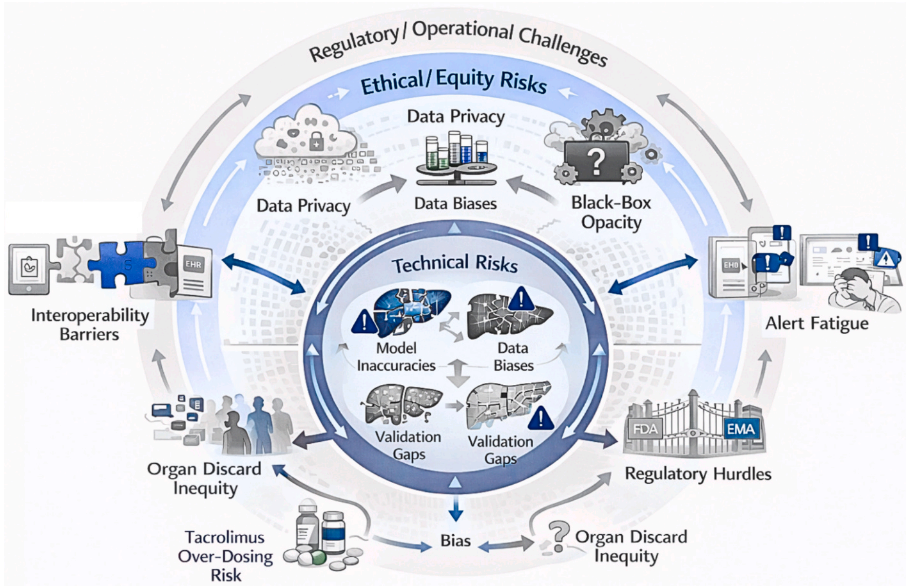

Fig. 2. Key risks and challenges in implementing digital twins for organ transplantation. Concentric layers depict interconnected technical, ethical/equity, and regulatory/operational barriers, emphasising needs for validation, fairness audits, and human oversight to ensure safe translation.

search scope. Systematic reviews with explicit eligibility criteria, formal quality assessment, and meta-analysis, where appropriate, would provide more rigorous evidence synthesis for specific questions, such as the efficacy of model-informed tacrolimus dosing.

Second, the field is evolving rapidly, and much work exists in preprint form, conference abstracts, or industry documentation that has not undergone peer review. We intentionally included such sources to capture the frontier of development, but this introduces uncertainty about validity and reproducibility. Findings from preprints should be considered preliminary until confirmed by peer-reviewed publication and independent replication. Industry-reported capabilities, whilst illustrative of technological potential, may not reflect performance in independent, prospective clinical studies.

Third, evidence quality varies widely across the applications we surveyed. Model-informed dosing for tacrolimus is supported by various prospective studies and clinical trials, whereas immune digital twins and whole-patient twins remain largely conceptual. We attempted to characterise maturity for each application, but readers should exercise discernment about the strength of evidence supporting different claims. Our narrative format does not include formal grading of evidence quality, which would enhance transparency.

Fourth, we did not conduct primary data collection or quantitative synthesis. Our review is interpretive and relies on the author's judgement in selecting and synthesising sources. Different reviewers might emphasise different applications or reach different conclusions about priorities. Our proposed roadmap reflects our assessment of feasibility, potential impact, and readiness, but these are value-laden judgements that are open to reasonable disagreement.

Fifth, we focused primarily on solid-organ transplantation in adults, with limited attention to haematopoietic stem cell transplantation, paediatric populations, or resource-limited settings. Digital twin applications and implementation barriers may differ substantially in these contexts. The generalisability of our findings and recommendations should be assessed with caution when considering other transplant types or settings.

Sixth, our discussion of ethical, regulatory, and operational considerations is necessarily high-level. Detailed analysis of regulatory pathways, health economic evaluation, implementation science, and ethics would each merit dedicated reviews. We aimed to flag important issues and principles without exhaustively addressing them.

Finally, this review was conducted primarily from a clinical and technological perspective. Patient and caregiver perspectives on digital twins, their information needs, concerns about privacy and algorithmic decision making, and preferences for involvement in twin-governed care are underrepresented in the current literature and in our synthesis. Future work should centre patient voices in digital twin design and evaluation.

10. Conclusion

Digital twins offer a significant opportunity to improve decision-making in the transplant journey, from preoperative risk assessment to lifelong graft surveillance. As technological solutions enabling precision medicine, digital twins provide the computational infrastructure necessary to deliver truly individualised care tailored to each patient's unique biological, genetic, and clinical characteristics. By combining a deep understanding of organ biology with real-time physiological, biochemical, and molecular data, digital twins can personalise care in unprecedented ways.

While the field is progressing from concept to early applications, such as model-informed tacrolimus dosing and liver virtual twins, most implementations remain digital shadows rather than fully developed twins with closed-loop control. Evidence of improved patient outcomes remains limited, largely confined to simulation studies and reports rather than peer-reviewed trials. Validation across diverse populations to demonstrate benefits in rejection rates, graft survival, and patient quality of life is crucial for broader adoption.

The integration of artificial intelligence and machine learning represents a critical enabler of digital twin functionality, providing the analytical capabilities necessary to process complex, multimodal data streams and generate actionable predictions. Future development must prioritise explainable AI approaches that maintain transparency in clinical decision-making, address algorithmic bias to ensure equitable access to twin-enabled precision medicine, and establish regulatory frameworks appropriate for adaptive, learning systems.

Challenges related to data interoperability, model transparency, and regulatory concerns must be addressed. We propose a pragmatic roadmap, beginning with high-value applications that establish data pipelines and build trust while generating evidence. Immediate targets include organ quality assessment during machine perfusion and model-informed tacrolimus dosing.

Success will be evaluated through technical metrics and patient-centred outcomes such as graft survival and equitable access to benefits. Continuous evaluation via trials and fairness audits will be vital for minimising potential harms. Collaboration among transplant clinicians, computer scientists, AI researchers, and other stakeholders is essential for navigating complexities. Transplantation's unique characteristics position it well to test digital twins and serve as a model for wider healthcare applications. As a precision-medicine technology, digital twins have the potential to transform transplantation from a field relying on population-based protocols to one delivering truly individualised care. By prioritising validation and patient safety, the transplant community can harness the potential of digital twins to enhance the lives of donors, recipients, and clinicians alike.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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