A TIMED COLOR PETRI NET MODEL FOR THE PRE-DIALYSIS CLINICAL PATHWAY IN CHRONIC KIDNEY DISEASE: COMPARISON WITH CONTEMPORARY PREDICTIVE MODELLING APPROACHES

Sofoklis Christoforidis

Athanasios Thomopoulos

Efstathios Titopoulos

Assoc. Prof. PhD Eng. Boriana Ilieva

Assoc. Prof. PhD Eng. Georgi Stanchev

Technical University of Sofia, Sofia, Bulgaria

Eleni Kromitoglou

Democritus University of Thrace, Kavala, Greece

Maria Ioulia Chatziprodromou, MD

General Hospital Drama Greece

Abstract. Patients with advanced Chronic Kidney Disease (CKD) require continuous surveillance, risk assessment, education, shared decision-making with healthcare providers, preparation for kidney replacement therapy, and timely management of clinical deterioration. The majority of computational work in CKD has focused on predicting the time to end-stage renal disease (ESRD) and the initiation of renal replacement therapy (RRT). Currently, limited computational research has formally modelled the complex processes of healthcare delivery that occur before and during preparation for RRT. In parallel, emerging approaches to occupational health and safety (OSH) emphasize dynamic, individualized risk assessment based on the integration of workplace environmental measurements, occupational exposure data, and employee health information obtained through periodic and prophylactic medical examinations. Such approaches offer the potential to continuously update employee-specific risk profiles and support timely preventive interventions in response to changes in workplace conditions or health status.

This paper presents a timed Colour Petri Net (CPN) model of the pre-dialysis clinical pathway and compares its analytical scope with contemporary predictive and digitally supported models of care for patients with CKD. The model represents patient attributes as tokens of different colours and incorporates the principal kidney replacement therapy options, including haemodialysis, peritoneal dialysis, transplantation and conservative management, together with relevant healthcare resources, treatment preparation delays, and pathways leading to dialysis initiation. The ordinary projection of the net comprises 27 places and 24 transitions. The analytical scope of the CPN is compared with that of KFDeep, a longitudinal deep-learning model for predicting CKD progression, which reported area under the receiver operating characteristic curve (AUROC) values of 0.946 for internal validation and 0.805 for external validation (Ma et al., 2025).

Unlike predictive models, which estimate the probability of CKD progression, process models characterize responses to patient needs, healthcare resource constraints, reachable states, and potential failures of planned care. A hybrid predictive-process architecture is therefore proposed to support patient-specific, resource-aware clinical decisions and dynamic, individualized occupational health and safety risk assessment by integrating workplace measurements and findings from medical examinations to automatically update employee risk profiles and guide preventive interventions.

Keywords: pre-dialysis care, dialysis, kidney replacement therapy, formal verification, healthcare simulation, risk assessment.

Introduction

CKD is a long-term condition that progresses in a stepwise manner from advanced CKD to end stage renal failure (ESRF) through a series of surveillance appointments and treatment preparation. It is portrayed as a clinical process that requires coordinated monitoring and assessment of a patient's renal function, together with a range of compensatory treatments to manage complications, as well as stabilization and management of existing prescribed medications. Underlying these complex treatment approaches is a patient-centered approach to care delivery (kidney disease: Improving Global Outcomes [KDIGO] CKD Work Group, 2024). Completion of assessment for renal replacement therapy or for conservative management of kidney failure is recommended to begin at least a year before the expected need for treatment (National Institute for Health and Care Excellence [NICE], 2018).

Moving on from this type of single event prediction, representing the clinical process of a patient being treated for advanced CKD passing through to a failure of kidneys and

progressing to need for renal replacement therapies (RRT) in a computational model is a complex challenge using conventional prognostic models. Tracking a number of different variables as they change over time, considering the patient's treatment choices, carrying out repeated clinical assessments, preparing for different eventualities, managing limited healthcare resources and dealing with unexpected events such as a patient's sudden deterioration all have to be captured in a clinically sensible computational model. Working with a single eGFR threshold for initiation of dialysis is not appropriate as there are a number of different factors that determine a patient's symptoms and the full range of biochemical abnormalities and a patient's fluid status, as well as shared clinical decision making with the patient (NICE, 2018).

Despite the increasing number of studies using advanced machine-learning methods for diagnosis and prediction of CKD progression, recent reviews on the subject found good discriminatory performance, but also several limitations of the previous studies, including being based on retrospective data, using very heterogeneous methods, limited external validation, lack of explainability and most importantly limited evidence of clinical usefulness in prospective setting (Eskandar, 2026; Van de Putte & Speeckaert, 2026). The present study addresses a different, complementary problem and models the process of a patient going through a preparation for a potential kidney failure under constraints of time and resources in a clinical setting.

Methodology

Study Design and Clinical Abstraction

A formal process-modelling study was completed to develop a timed CPN to model the pre-dialysis process. The model was developed as a conceptual and analytical representation of the pre-dialysis process, rather than as a decision support tool or a clinical decision support system. The main structures and elements of the principal pathway were derived from KDIGO 2024 and NICE NG107 guidelines for the pre-dialysis process. A further 'Urgent' pathway was developed to model patient deterioration resulting in an urgent start of dialysis.

In this abstraction, we distinguish between the clinical need for preparation of a patient with end-stage renal disease for kidney replacement therapy and the operational readiness for that patient to start on this form of treatment. For example, a patient who is determined to need preparation for kidney replacement therapy may not yet have vascular access formed, access matured, PD catheters prepared or even be on the waiting list for a kidney transplant and

associated work-up still to be completed. The model can then assess whether the health care system is able to complete all the required preparation before urgent treatment becomes required.

Colour Petri Net Specification

The design of the net pathway CPN = (P, T, A, Sigma, V, C, G, E, I) has been detailed. P represents the places of a net, T the transitions, A the arcs, Sigma the color set, V a set of variables, C the color function for places, G the transition guard function, E the arc function for arcs, and I the initial marking function. The design of a patient as a colored token c_p = (id, stage, eGFR, ACR, symptoms, modality, access, status, tau) allows patients to be distinguished from each other even when they are in the same place. The Access Preparation place contains tokens representing patients scheduled for planned arteriovenous fistulae, patients with created fistulae and patients scheduled for planned PD access. All these patients are modeled without adding more places to the design of the net pathway. Simulation time tau is registered for each patient.

Patient, Resource, and Temporal Subnets

The ordinary projection contains 19 patient-state places and eight resource places making a total of 27 places plus 24 main transitions. The resource places are allocated to nephrologists, CKD nurses, dietitians, vascular surgeons, PD nurses, transplant teams and dialysis teams and lastly to dialysis capacity places. The transitions requiring a resource can only fire when the patient and resource tokens are available simultaneously. The reusable resource tokens are returned after a transition has been fired.

In this scenario-based model, time is modeled as one simulation unit, equal to one day. The parameters describing delays such as review times, referral times, patient-education time, decision time for dialysis modality, time to access planning, time to access maturation, time to prepare a patient for PD, time for transplant work-up and time to start treatment are all modeled as scenario parameters and not as clinical-standards. In empirical work these would be replaced by appropriate distributions, estimated from real pathway data.

Transition Guards and Outcomes

Transition guards represent the eligibility conditions encoded in the patient-token color. Modality-specific transitions select the correct treatment, access transitions indicate whether it is HD or PD preparation, and dialysis initiation uses a single clinical abstraction that takes into account more than just the eGFR value. The intended methodological principle is to follow NICE guidance for the symptoms, biochemistry, fluid overload, kidney function and shared decision making required for treatment initiation (NICE, 2018). The Final outcome places represent the four types of treatment: planned dialysis, unplanned dialysis, pre-emptive transplantation and conservative management.

Structural Verification

To support conventional Petri-net analysis, a colored Petri-net model was projected onto 27 x 24 input and output incidence matrices, Pre and Post. From the structural incidence matrix C = post-Pre one finds that C has rank 18. As the number of P-invariants equals the dimension of the right-kernel (invariant space) of C^T, one finds a nine-dimensional invariant space from C^T y = 0. One of the P-invariants corresponds to a patient, whereas the remaining eight P-invariants correspond to P-invariants describing re-usable health care resources. T-invariants were computed from Cx = 0 and form a six-dimensional algebraic null space. A clinically meaningful non-negative invariant was found which describes a surveillance cycle (i.e., clinical review, stable assessment, and return to surveillance).

As an example of why we need to use coloured-state analysis of projected PNs, some clinically very relevant transitions have zero ordinary incidence in the projected PN because they consist of a patient that is already in a given structural place of the PN, and the change consists in the change of the token's color, i.e. the patient stays in the same place but the clinically relevant property of the patient changes, e.g. in the Access Preparation place AVF_Planned becomes AVF_Created.

Comparator Selection and Evaluation Framework

We did not find any recent formal model addressing all aspects of end-to-end pre-dialysis care including treatment choice within given resources in given time. Therefore, we selected KFDeep as the most relevant, state-of-the-art, predictive model, using longitudinal health record data and external validation. The corresponding study included 4,587 patients in development-related datasets and 934 patients in an external prospective cohort, reaching AUROCs of 0.946 (intern) and 0.805 (extern) (Ma et al., 2025). Furthermore, we also included

DeepOmix-FLEX as another multimodal predictor model and PREPARE NOW as a workflow-oriented model for digital care in chronic diseases (Green et al., 2021; Qiao et al., 2025).

The models were compared along five dimensions: 1) patient representation, 2) treatment-pathway coverage, 3) temporal behavior, 4) healthcare-resource representation, and 5) analytical capability. Predictive accuracy was not used as a performance measure for the CPN as the models answer different questions: predictive models compute P(Kidney Failure | X_0:t) while process models check whether a given initial marking M_0 can be reached from a subsequent marking M_t by means of an admissible transition sequence. Hence, we can only assess whether these models are complementary or not.

Comparative Analysis

KFDeep (Ma et al., 2025) captures the main advantage of modern longitudinal machine learning models: to estimate the risk of progression for individual patients on the basis of their repeated clinical measurements. To this end, the model uses age, sex, eGFR, urine albumin-to-creatinine ratio, albumin, calcium, phosphorus, and bicarbonate. Importantly, the model was externally validated on a second dataset and performed well on this “completely independent” data set. In contrast, DeepOmix-FLEX (Qiao et al., 2025) is a multimodal prediction model for CKD progression that incorporates clinical, proteomic, metabolomic, and pathology-image data. The mean AUC for predicting CKD progression of this model was 0.887. Here, DeepOmix-FLEX can discover complex relations between input variables and the prediction variable that a designer of a CPN would not think of.

The CPN can also be used to model the consequences of identifying a patient at risk of kidney failure such as, the patient’s need for education on various treatments, the healthcare provider’s choice of treatment modalities, the availability of staff to manage the selected treatment modalities, the availability of vascular access for the patient on peritoneal dialysis, the preparation of the patient for peritoneal dialysis, the initiation of work-up for a possible kidney transplant, the preparation of the patient for treatment, and the deterioration of the patient’s condition. The P-invariants of the CPN can be used to verify the model for patient conservation and for reusable resources’ conservation, while the transition structure of the CPN can be used to verify reachability, boundedness, liveness, and future distinguishability properties.

PREPARE NOW is an intermediate approach to modeling process for patients with CKD. The tools developed as part of the research integrate CKD risk assessment with nurse

case management and patient values clarification, in addition to process tracking for treatment preparation, and documentation of patient preferences for modalities of care. The work was piloted at four CKD clinics and identified 1,032 unique patients, 243 of whom were at high risk of kidney failure within two years (Green et al., 2021).

Discussion

There is considerable value in distinguishing between using a model to predict an outcome and using a model to manage processes within a healthcare system. Predictive models estimate if and when a patient will progress to end-stage kidney failure, whereas timed Colour Petri Nets (CPNs) represent the sequences of patient-centered activities required, the resources needed to deliver care, and whether planned interventions can be completed before clinical deterioration occurs. Such process models are particularly valuable in advanced CKD, where effective care depends not only on predicting disease progression but also on coordinating treatment preparation, patient preferences, healthcare resources, and timely interventions.

The formal CPN model makes its assumptions, transition conditions, resource constraints, and time delays explicit. In contrast, machine-learning models derive predictive relationships from data and can provide individualized estimates of clinical risk, although limitations in prospective validation and methodological consistency remain (Eskandar, 2026; Van de Putte & Speeckaert, 2026). The two approaches are therefore complementary: predictive models estimate the likelihood of an adverse outcome, while process models represent the operational responses and constraints associated with that outcome.

This distinction also provides a basis for extending hybrid predictive-process modelling to occupational health and safety risk assessment. Integrating workplace environmental monitoring with occupational health surveillance can support the identification of harmful exposures, early detection of work-related health problems, and continuous review of preventive measures (Titopoulou et al., 2024). A dynamic approach could incorporate relevant workplace measurements, occupational exposure data, and findings from periodic medical examinations into an individualized employee risk profile. Changes in exposure conditions, examination findings, or working practices would trigger predefined reassessment rules and automatically update the corresponding risk classification, supporting timely preventive interventions and appropriate workplace adjustments. This automated approach represents a proposed development of existing risk assessment and health surveillance practices and would

require validated decision rules, data protection, medical confidentiality, and appropriate professional oversight.

Within such architecture, predictive models could estimate the likelihood of adverse health outcomes, while a timed CPN could represent the sequence of preventive actions, medical assessments, workplace interventions, responsible personnel, resource availability, and required completion times. Transition guards could be updated using validated risk indicators and predefined decision thresholds, allowing the model to represent changes in risk and assess whether appropriate preventive actions can be completed within the required time. Such a framework complements the CKD application by demonstrating how predictive-process modelling supports both patient-centered clinical pathways and individualized occupational risk management. Its implementation requires validated decision rules, reliable measurement data, appropriate handling of uncertainty, data protection, medical confidentiality, and oversight by competent occupational health and safety professionals.

Future hybrid architecture therefore combines longitudinal risk prediction with a formally specified process model. In CKD, updated patient-specific risk estimates could inform clinical surveillance and preparation by kidney replacement therapy. In OSH, updated employee risk profiles could inform reassessment priorities and preventive interventions in response to changes in workplace exposure or health findings, in both applications, the predictive component would inform risk estimation, while the process component would represent the actions, constraints, and possible outcomes associated with managing that risk.

Limitations

Several limitations must be acknowledged. First, the CPN presented here remains a conceptual model that has not yet been validated against real patient pathways. Structural verification does not establish clinical validity, predictive validity, or improved patient outcomes. Second, the timing parameters as illustrative and do not reflect the variability of actual waiting times. Empirical implementation would require validated time distributions and sensitivity and uncertainty analyses.

Third, the current patient-token colour encoding represents only a subset of clinically relevant characteristics and does not fully account for multimorbidity, frailty, mortality risk, acute hospitalization, treatment contraindications, educational needs, or changes in patient preference. Fourth, representing healthcare resources as tokens simplifies workforce constraints, including shift patterns, competing demands, cancellations, geographical

accessibility, and resource substitution. Fifth, the ordinary incidence matrix does not capture clinically meaningful changes in token attributes when the structural place remains unchanged; color-refined state-space analysis is therefore also required.

The proposed OSH application is a methodological extension rather than a demonstrated capability of the current CKD model. Its practical value would need to be assessed through a separate implementation incorporating representative workplace measurements, occupational exposure information, relevant medical surveillance findings, validated risk criteria, and appropriate reassessment procedures. Automatic updates should be subject to data-quality checks, defined rules, and suitable professional oversight rather that being interpreted as autonomous medical diagnosis or an unrestricted determination of fitness for work.

Finally, the comparison with KFDeep, DeepOmix-FLEX, and PREPARE NOW is methodological rather than a head-to-head performance evaluation. Predictive accuracy cannot be directly compared with reachability, invariants or workflow coverage. Future research should validate the CPN against observed clinical pathways, incorporate empirical waiting-time distributions, integrate predictive models of CKD progression, and evaluate clinical and operational outcomes. A separate OSH implementation should similarly evaluate the reliability if dynamic risk updates, the timeliness of preventive interventions, and the transferability of the approach across different workplaces.

Conclusion

The proposed timed Colour Petri Net provides a formal and resource-aware representation of the pre-dialysis clinical pathway in CKD. Unlike contemporary predictive models, such as KFDeep and DeepOmix-FLEX, which estimate individual risks of disease progression, the CPN represents the sequence of clinical activities, treatment decisions, resource constraints, preparation delays, and potential deterioration that influence the delivery of kidney replacement therapy. The most promising approach is therefore to integrate predictive models with timed, formally analyzed process models to support patient-specific, resource-aware decision making.

This hybrid predictive-process architecture also offers a methodological basis for extending dynamic risk assessment to occupational health and safety. By integrating workplace environmental measurements, occupational exposure data, and relevant findings from periodic and prophylactic medical examinations, future systems could automatically update employee-specific risk profiles when new information or changes in working conditions warrant

reassessment. Such updates would support timely preventive interventions, provided that validated assessment criteria, data protection, medical confidentiality, and appropriate professional oversight are ensured.

Although the current CPN remains a conceptual model requiring empirical validation, its formal structure provides a foundation for further development of decision-support systems that combine predictive analytics, time-dependent process modelling, and individualized risk assessment. Future research should evaluate the model against real clinical pathways and investigate the implementation of the proposed OHS extension, including the reliability of automated risk updates and their effectiveness in supporting preventive action. This integrated approach will contribute to more proactive, transparent, and resource-aware management of both clinical care and occupational health and safety risks.

REFERENCES

ESKANDAR, K. (2026). Artificial intelligence in chronic kidney disease: Early detection, risk prediction, and personalized treatment strategies. World Journal of Nephrology, 15(2), 117719. https://doi.org/10.5527/wjn.v15.i2.117719

GREEN, J. A., EPHRAIM, P. L., HILL-BRIGGS, F., ET AL. (2021). Integrated digital health system tools to support decision making and treatment preparation in CKD: The PREPARE NOW study. Kidney Medicine, 3(4), 565-575.e1. DOI: 10.1016/j.xkme.2021.03.009

KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES (KDIGO) CKD Work Group. (2024). KDIGO 2024 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International, 105(4S), S117-S314. https://doi.org/10.1016/j.kint.2023.10.018

MA, J., WANG, J., LU, L., SUN, Y., FENG, M., SHEN, P., JIANG, Z., HONG, S., & ZHANG, L. (2025). Development and validation of a dynamic kidney failure prediction model based on deep learning: A real-world study with external validation [Preprint]. arXiv.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE. (2018). Renal replacement therapy and conservative management (NICE Guideline NG107). https://www.nice.org.uk/guidance/ng107

TITOPOULOU, M., PANCHEVA, V., STAYKOVA, J., & AGOVSKA, A. (2024). Enhancing Workplace Productivity and Health: The Impact of Preventive Medical Screening for Employees in Bulgaria. Journal of IMAB - Annual Proceedings, Supplement 3. DOI:10.5272/jimab.2024Supplement3

QIAO, Y., ZHOU, H., LIU, Y., CHEN, R., ZHANG, X., NIE, S., HOU, F. F., ZHAO, Y., XU, X., & ZHAO, L. (2025). A multi-modal fusion model with enhanced feature representation for chronic kidney disease progression prediction. Briefings in Bioinformatics, 26(1), bbaf003. https://doi.org/10.1093/bib/bbaf003

VAN DE PUTTE, L., & SPEECKAERT, M. M. (2026). Applications of machine learning for early diagnosis and prognosis of chronic kidney disease: Current evidence. Diagnostics, 16(15), 2354. https://doi.org/10.3390/diagnostics16152354

Sofoklis Christoforidis

ORCID iD: 0009-0000-9818-8264

Technical University of Sofia, Bulgaria

Email: sofoklis.christoforidis@gmail.com

Athanasios Thomopoulos

ORCID iD: 0009-0004-5385-0663

Technical University of Sofia, Bulgaria

Email: athanasios.thomopoulos@gmail.com

Efstathios Titopoulos,

ORCID iD: 0000-0003-4084-1675

Technical University of Sofia, Bulgaria

Email: titopoulos@lot-consult.com

Dr. Georgi Stanchev, Assos. Prof.

Department „Fundamentals and Technical Means of Design”,

Technical University of Sofia,

Bulgaria

E-mail: gstanchev@tu-sofia.bg

Dr. Assoc. Prof. Boryana Petkova Ilieva-Mihailova,

Department „Fundamentals and Technical Means of Design”,

TU-Sofia , Bulgaria

E-mail: bilieva@tu-sofia.bg

Eleni Kromitoglou

ORCID iD: 0009-0000-2789-1112

Democritus University of Thrace, Kavala, Greece

Email:elkromi@mst.duth.gr

Maria Ioulia Chatziprodromou, MD

ORCID iD: 0009-0001-4494-3380

General Hospital Drama Greece

Email: marilitablack@gmail.com