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Editorial

Artificial Intelligence and Vitamin D Deficiency: Opportunities and Challenges for Clinical Translation in Chronic Diseases

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Vitamin D (VD) is a fat-soluble prehormone with pleiotropic effects extending beyond the well-established bone metabolism. Association studies demonstrated that VD deficiency exerts important effects on cancer, cardiovascular risk, respiratory conditions, infections, diabetes, neurological and autoimmune disorders, and other chronic diseases. Despite the extensive research on VD, its pathogenetic, prognostic, and/or therapeutic roles across different diseases remain incompletely defined, and no standardized clinical procedure has yet been established. Heterogeneous study designs, variability in serum 25-hydroxyvitamin D (25(OH)D) thresholds, adequate supplementation regimens, and the complex interaction between VD and immune pathways contribute to the gap between strong biological plausibility and concrete translation in practical guidelines.

Numerous studies have focused on overcoming this complexity through the application of artificial intelligence (AI) and machine learning (ML). Owing to its ability to rapidly integrate multidimensional clinical, biochemical, and biological data and identify nonlinear relationships more efficiently than traditional statistical analysis, AI has been increasingly used in medicine. AI is particularly suited for studying VD status and overcoming the specific methodological challenges of VD research, including the marked interindividual variability in serum 25(OH)D levels, lack of universally accepted deficiency thresholds, and the dependence of VD status on the complex interplay among genetic, metabolic, immunological, environmental, and lifestyle factors. Unlike conventional statistical models, which often rely on linear correlations and predefined interactions, AI-driven algorithms can capture complex and multidimensional patterns, identify the most informative features, and uncover hidden interactions among variables that might otherwise remain unrecognized. These capabilities may facilitate the stratification of patients into subgroups with differing susceptibility to VD deficiency or variable responses to supplementation, thereby supporting a more precise and tailored clinical approach.

Initial evidence supporting the utility of AI for studying VD-related diseases has been acquired under diverse chronic and inflammatory conditions. In metabolic and cardiovascular contexts, artificial neural networks (ANNs) have been used to reveal a correlation between low VD levels and high blood glucose levels, a condition preceding the metabolic syndrome. Auto-contractive map (AutoCM) analysis has revealed that VD levels are inversely related to C-Reactive Protein (CRP) levels, i.e., low VD levels may predispose to inflammatory states increasing cardiovascular risk [1]. Similarly, ML algorithms such as Least Absolute Shrinkage and Selection Operator (LASSO) and elastic net can effectively predict VD deficiency in patients with hypertension and obesity and thus hold promise for targeted screening and preventive strategies [2].

Other supervised ML algorithms, such as random forest (RF), *k*-nearest neighbors (kNN), decision tree (DT), and support vector machine (SVM), are effective in assessing VD status in women suffering from endocrine and reproductive dysfunction, particularly that due to the polycystic ovary syndrome, revealing that a considerable percentage (>40%) of these women features low VD levels [3]. This outcome confirms the ability of AI to support individualized management under multifactorial conditions where VD contributes to disease expression rather than being the primary cause.

In the context of neurological disorders, an XGBoost algorithm–based ML model has effectively predicted the correlation of VD levels with the severity of poststroke neurological deficits, thus suggesting the prognostic value of these levels [4]. Other computational methods have proven useful in predicting cognitive decline in Alzheimer's patients with low circulating levels of VD after a four-year follow-up. In this case, low levels of VD may be associated with more rapid cognitive decline [5]. Allahyari *et al.* [6] used ANNs to identify complex relationships between individual characteristics and response to supplemental VD therapy, which would not have been immediately made apparent using linear statistical methods. A group of 619 pa-

Table 1. Summary of AI/ML models used in disparate conditions to analyze VD involvement.

Study	Disease/population (*n*)	AI/ML model	VD-related outcome	Main findings	Clinical interpretation	Limitations
Vigna *et al*. [1], 2019	Excess weight, obesity/309	ANN, AutoCM	Prognostic	Lower VD levels are associated with higher glucose levels and increased CRP	VD deficiency predicts metabolic and inflammatory risks	Small number for ANN, working population only, exclusion of under-40s, specific cohort (Italy)
Zhang *et al*. [4], 2022	Ischemic stroke/200	XGBoost	Prognostic	Lower VD levels are associated with more severe neurological deficits	VD level is a predictor of poststroke severity	Single-center cross-sectional retrospective study with a small sample size
Murdaca *et al*. [5], 2021	Alzheimer's disease/108	LASSO, ridge, elastic net, CART, RF	Prognostic	Low VD levels are predicted to accelerate cognitive decline (MMSE reduction)	VD deficiency is a prognostic marker of neurodegeneration	Gender-blind
Allahyari *et al*. [6], 2020	Adults receiving VD supplementation/619	ANN	Predictive/therapeutic	Baseline VD levels and cognitive scores predicted response to supplementation	Individual response to VD therapy can be predicted by AI	Gender-blind, poor predictive capacity for high responders, generalizability limited to age groups other than the adolescent or working age analyzed
Otani *et al*. [7], 2022	Digestive tract cancer/417	Multivariable adaptive regression splines	Prognostic/therapeutic	Optimal VD range is associated with improved recurrence-free survival	Personalized VD supplementation may improve cancer outcomes	Surgical stress, posthoc analysis, ethnic homogeneity, heterogeneity of diseases
De Sire *et al*. [8], 2022	Breast cancer/53	Multiple factor analysis (MFA)	Prognostic	Only 5.6% of test subjects had normal VD levels	VD deficiency correlates with osteoporosis risk	Small size for MFA, measurement quality, hypothetical/predictive nature, failure to evaluate VDR
McGuinness *et al*. [9], 2024	Breast cancer/208	CNN	Therapeutic	VD supplementation showed no significant chemopreventive effect	VD supplementation alone may not be effective as chemoprevention	Small sample, technical problems, cohort homogeneity, lack of data
Li *et al*. [12], 2022	HT/1303	XGBoost, logistic regression, SVM, kNN, DT	Diagnostic/predictive	Serum 25(OH)D levels ranked among relevant features in predicting HT risk	VD acts as a biomarker of disease risk in AI-driven stratification models	Reduced number, lack of diagnostic distinction and specific antibodies, missing immunological and biological factors

Diagnostic, AI used to classify or detect VD deficiency; Predictive, AI used to identify individuals at risk of a VD-related effect; Prognostic, AI used to estimate disease course or outcome severity in relation to VD levels; Therapeutic, AI used to model or predict response to VD supplementation.

AI, artificial intelligence; ML, machine learning; VD, Vitamin D; ANN, artificial neural network; CRP, C-Reactive Protein; AutoCM, Auto-contractive map; LASSO, Least Absolute Shrinkage and Selection Operator; CART, Classification and Regression Trees; RF, random forest; MMSE, Mini-Mental State Examination; MFA, multiple factor analysis; VDR, Vitamin D receptor; CNN, convolutional neural network; SVM, support vector machine; kNN, *k*-nearest neighbors; DT, decision tree; HT, Hashimoto's thyroiditis.

tients underwent standardized neuropsychological testing to assess various variables, including cognitive function and daytime sleepiness, after nine weeks of VD therapy. The cognitive function and baseline levels of 25(OH)D were found to be important predictors of changes in VD levels after supplementation [6]. This evidence supports the hypothesis that VD status influences disease progression and may have a prognostic role.

In oncology, AI has been used to identify optimal VD levels (18–28 ng/mL) associated with improved recurrence-free survival in patients with digestive tract cancer; therefore, correct VD supplementation may be crucial in these patients [7]. Conversely, a study on women with breast cancer assessed VD deficiency secondary to aromatase inhibitor therapy. Factorial analysis revealed that only 5.6% of these women had normal VD levels and bone health, highlighting the need for timely VD monitoring and correction to avoid subsequent alterations in bone health in this at-risk group [8].

A convolutional neural network (CNN) model analyzed the response to chemoprevention through VD supplementation in patients with breast cancer. The absence of significant differences between treatment and placebo groups suggested that supplementation alone is not beneficial as chemoprevention [9]. Together, these findings show how AI can be used to determine whether VD intervention is likely to be beneficial or have a marginal impact.

VD deficiency is strongly related to autoimmune and immune-mediated disorders. VD exerts immunomodulatory effects on innate and adaptive immune responses [10]; however, the related clinical findings remain fragmented and heterogeneous, largely because of the high content dependency of VD roles and the dependence on numerous variables beyond VD status alone. In this setting, AI-based models provide a powerful opportunity to identify subgroups of patients who can benefit from VD supplementation or not [11]. ML approaches have highlighted that circulating 25(OH)D levels could be used as a risk prediction factor in autoimmune diseases such as Hashimoto's thyroiditis (HT) [12]. This evidence can trigger the transformation of VD from a generic and broadly prescribed intervention into a precision medicine tool. Such observations are particularly relevant for autoimmune diseases and primary immunodeficiencies, in which case VD level is an easily measurable and modifiable factor with potential implications for disease severity, infection susceptibility, and long-term comorbidities.

Our aim is to shed light on the potential translational perspective of integrating AI into VD research to achieve direct implications for clinical practice and precision medicine (Table 1, Ref. [1,4–9,12]). AI-driven clinical management support systems could assist clinicians in identifying different risk groups, tailoring supplementation strategies, and monitoring treatment response. The growing body of evidence across metabolic, neurological, oncological, and immune-mediated disorders suggests that AI models are useful for standardizing VD research and applying the obtained insights in clinical medicine.

Despite the considerable potential of AI to decode the pleiotropic effects of VD, its application is not exempt from erroneous clinical estimations, the primary concern being the black-box nature of many ML models. Without explainable AI frameworks, clinicians may struggle to distinguish mere statistical correlation from biological causation. This difference is fundamental to understanding whether a low VD level is a causal factor of a chronic disease or is secondary to the same (reverse causality). Other limitations of AI applications may be related to a lack of standardization of VD levels and the analytical variability observed for data originating from laboratories using different methods. AI algorithms are highly sensitive to residual confounding. Given that VD levels are deeply intertwined with lifestyle, Body-Mass Index (BMI), and socioeconomic status, a model failing to capture these interactions might incorrectly attribute disease risk to VD deficiency. Moreover, AI reliability heavily depends on the quality, size, and representativeness of training datasets. Many available studies rely on retrospective data or small and heterogeneous samples, which leads to potential bias, overfitting, and limited reproducibility across populations.

To move toward precision medicine, AI models should be methodologically validated to support clinical evaluation rather than replace it. Future research should prioritize prospective study designs with larger and more diverse cohorts, rigorous external validation, the transparent reporting of model architecture, and the integration of explainability tools to facilitate translation into clinical decision support systems.

Author Contributions

SG and GM designed the research study and reviewed the paper. FN and EZ performed the data collection and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest. Given his role as the Guest Editor and Editorial Board member, Dr. Giuseppe Murdaca had no involvement in the peer-review of this article and has no access to information regarding its peer review. Given his role as the Guest Editor, Dr. Sebastiano Gangemi had no involvement in the peer-review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Graham Pawelec.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGpt-5.2 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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