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MOLECULAR QUANTUM AND LOGIC PROCESS OF CONSCIOUSNESS—VITAMIN D BIG-DATA IN COVID-19—A CASE FOR INCORPORATING MACHINE LEARNING IN MEDICINE

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ABSTRACT
There are unique relations between statistics and logic operating in neural networks in the human brain. Like machine learning, big data and artificial intelligence (AI) techniques could emulate human brain functions rapidly and assist healthcare decisions, especially in emergencies like COVID-19. We explore published positive modulatory effects of vitamin D on the human immune system from randomized control clinical trials (RCTs) and meta-analyses taken as an example. The analysis confirmed a robust negative correlation between serum 25(OH)D concentration with increased susceptibility to symptomatic SARS-CoV-2, complications, hospitalization, and deaths. Instead of using available such data in mid-2020, regulators relied upon RCTs from big pharma. Utilizing advanced Machine Learning paradigms using cleaned data would have expedited proper decision-making, better guidance on patient management, and approval of cost-effective early therapies like vitamin D and calcifediol, reducing the cost of care and millions of hospitalizations and deaths from SARS-CoV-2. Using Catuskoti logic in AI, broader than Boolean logic would have enhanced unbiased decision-making and developed data-driven algorithms to control outbreaks. Scientific evidence existed in mid-2020 that vitamin D and calcifediol rapidly boost the immune system, thus preventing SARS-CoV-2-related complications and deaths. However, statistical misconceptions, lack of broader vision, and failure to use big data analysis and machine learning approaches prevented using generic agents as prophylactic and adjunct therapies. We present the argument for hypothesis generation in conjunction with innovation in machine learning, using Catuskoti-based XOR and XNOR circuits as a solution to expedite the categorization of vulnerability, developing practical algorithms, and rapid approvals of repurposed drugs for future pandemics. Such data-driven analyses through machine learning programs minimize conflicts of interest and expedite decision-making. In the future, big data can be analyzed using desktop computers, facilitating prompt and proper decision-making and expedited drug approvals, especially for generics. This approach will better manage future epidemics and pandemics—cost-effective early therapeutic interventions, preventing complications, hospitalizations, and deaths, and reducing healthcare burden and cost.

KEYWORDS: 25(OH)D; pandemic; randomized-controlled trial (RCT); SARS-CoV-2, Artificial intelligence.

KeyPoints
This manuscript explores the rapid realization of benefits through integrating vitamin D big data into artificial intelligence/machine learning, offering a paradigm for expedited medical decision-making and policy formulation. Leveraging advanced deep learning techniques, we propose synthesizing extensive data sets, enabling the approval of repurposed, cost-effective compounds. This would facilitate economically sustainable policies and algorithms that directly benefit patients. This innovative approach improves clinical outcomes by reducing complications and fatalities, mitigating burnouts among healthcare workers, and lowering overall healthcare costs. Big data analyses substantiate the hypothesis correlating vitamin D deficiency with susceptibility to COVID-19, providing a foundation for machine learning algorithms to employ logic beyond traditional Boolean methods. By incorporating the Catuskoti tetralemma, these algorithms can swiftly unravel innovative, cost-effective patient management strategies and streamline drug approvals,

laying the groundwork for more effective responses during future epidemics and pandemics.

1.0 INTRODUCTION

The COVID-19 pandemic has uncovered several potential faults in scientific decision-making processes. Western nations were unprepared for a pandemic despite having multiple departments and institutes funded by taxpayers to prepare for such an eventuality. Divisions and a hiatus of knowledge exist between scientists and medical professionals vs. decision-makers—health administrators and political authorities—regarding the pertinent understanding of biological and immunological connections (innate and adaptive) and modulation of over 1,200 key genes by vitamin D as well as coronaviruses like SARS-CoV-2 that hijacks the immune system for its advantage. The lack of this led to suboptimal decision-making, orchestrated by inherent conflicts of interest of various parties, and the failure to explore existing global data, clinical experience, and published clinical outcomes.[1]

It was evident from early 2020 that effective remedies implemented by non-western countries were rejected and refused to be adopted by agencies in Western countries. Ironically, despite vast published data sets, this dichotomy even exists today. We also aimed to seek reasons for lacking a logical base for decision-making, partly because of the mentality of using Boolean logic leading to decision-making. In addition to unbiased interpretation of clinical study data, we explored the relationship of the analytical base of mathematical logic, statistics, and scientific data.[2,3]

Boolean logic is based on the binary data science equivalent of the law of the excluded middle. This logic has been extensively used to build machine learning and algorithms that approach the human capacity to see patterns rapidly. Moving from finite automata to fuzzy logic helped to capture some complex operations. Still, it failed to cover a complete spectrum of scenarios used in control space where Catuskoti or Thrikoti logic could help. One example related to medicine is the COVID-19 emergency, with little prevailing relevant previous data. In these circumstances, it is crucial to use Big Data to consolidate evidence, including experts and machines, to perceive correct patterns. We will begin referring to the Indian forms of logic, which we call the Nalanda Paradigm.[4]

1.1 The Catuskoti logic, Gödel, and Turing

We refer to logical approaches used by ancient Buddhist logicians (Catuskoti, Dignaga's trilemma of relations, and inference for self) and focus on Catuskoti tetralemma as it poses a logical system that solves the limitation of Boolean logic in data science, including machine learning, today. The following is a description of the premises in Catuskoti logic. This includes the binary logic familiar in the West but expands it to include two additional logical conclusions. Together, they are: A is true; B (not A) is true; Both A and B are true, and Neither A nor B is true.

The options (a) and (b) above form the traditional logic of the excluded-middle (Boolean logic). The binary (or Boolean logic) is incomplete and not exhaustive. The other logical systems accompanying Catuskoti are exceptions due to their specificity (Dignaga's trilemma involving the Universe and the inference for self-involving controlled experiments, thus "closed" systems). This incompleteness is best exemplified by referring to Gödel's Theorem. Gödel's theorem proved two statements regarding a system of mathematical axioms.

1. Incompleteness: Failure to capture all statements within the system (S) within the formulas of the system. Goedel demonstrated that true self-contradictory statements could be made (e.g., empirically evident). However, this is undecidable using the axioms due to the contradiction (both provable and not or both A and not A are true). Excluding factual contradictory statements makes the system incomplete.
2. Inconsistency: Consistency means no contradictions using the system S. Yet it is incomplete (according to the proof above), which means there is at least one contradiction using the axioms. Thus, the set cannot prove its consistency.

Gödel's theorem applies to Boolean (or binary) logic but not Catuskoti. The third premise of Catuskoti, both A and B, is the truth, not a contradiction, and is thus a solution to Gödel's paradox. The importance of Catuskoti logic is that it is complete. The four options described above are not only mutually exclusive but exhaustive as well. Regarding Catuskoti, note that A (option a) and B (option b) each exclude the other entirely and form an exclusive OR (X-OR) relationship. In contrast, options c (both A and B) and d (neither A nor B) of Catuskoti form their logical (binary) complement (X-NOR). These logical gates are depicted in Tables 1 and 2 below.[2]

Table 1: Depiction of XOR error-correcting gate demonstrating the equivalent of A or Not A (B) but not both in Catuskoti:

A	B	(A⊕B)
0	0	0
1	0	1
0	1	1
1	1	0

Table 2: Depiction of XNOR error-correcting gate demonstrating the equivalent of both A and not-A (B) or Neither A nor Not A (everything else or exceptions) in Catuskoti.

A	B	~(A⊕B)
0	0	1
1	0	0
0	1	0
1	1	1

Another important concept of causation lacking in a linear model is cycles accepted in ancient models of the East, and more recent models include systems theory,[5] incorporating concepts in thermodynamics, homeostasis, and feedback. Systems theory can incorporate events at any level (e.g., in biological systems up to social and organizational). This is a fundamental concept of diseases, where the condition is an imbalance caused by a perturbation introduced to a system in equilibrium.

For example, a recursion between logic gate XNOR (in which X, Y, Z, etc. are options in d) and XOR (X, Y, Z, being recursively promoted to option b in the XOR gate in which they are tested against an index variable, e.g., vitamin D level) is an example of such a cycle as well.

1.2 Chatuskoti (Quantum logic) in the form of XOR-XNOR recursion in the Central Nervous System

There are proposals at the level of quantum gravity connecting information/ consciousness to Quantum processes.[2,6] Raju,[3] demonstrated that Catuskoti logic was equivalent to Quantum Logic. Penrose,[2] proposed that the information in quantum processes fundamentally involved consciousness. His reasoning originated in the limits placed on machine logic by Gödel's theorem. Subsequently, Penrose and Hameroff,[7] explored consciousness and quantum revolutions in anesthesia. This research uncovered that tubulin molecules in microtubules of cortical pyramidal cells could fulfill this function. Later experiments confirmed information processing levels, from tubulin helices to π-bonds between tubulins. The π-bond resonance is postulated to access underlying quantum fluctuation, forming Planck-level information processing.[7]

This evidence is congruent with likely Catuskoti-like logic that could be postulated to occur in mammalian brains. The cortex is divided between the left and right hemispheres, performing complementary cognitive processes.[8,9,10] These complementary functions of the hemispheres could be mediated at the level of cortical modules, either due to input/output differences or complementary cytoarchitecture at the level of the cortical module (a canonical circuit at the cortical level). This information is processed and crucially mediated by the intrinsic involvement of the pyramidal cells in a recurrent circuit (figure 1).

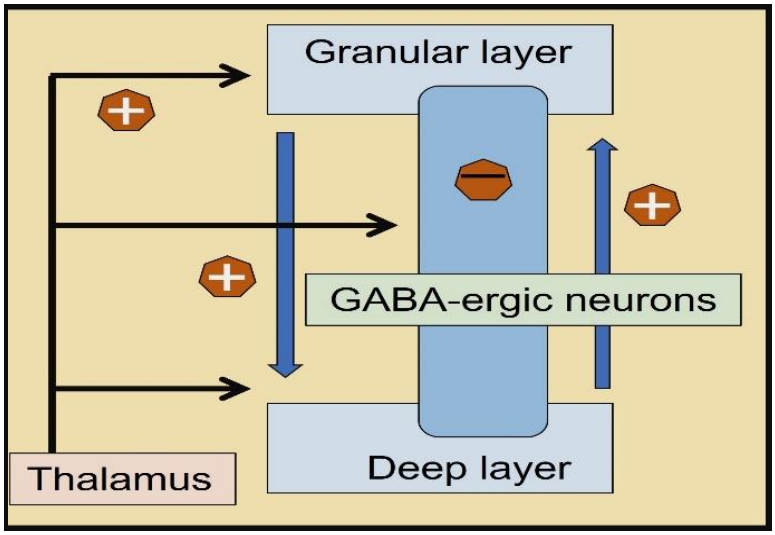

Figure 1: Illustrates a cortical canonical circuit that is considered to occur in a generic cortical module (a 2x2x4 mm^3 volume, thus around 85,000 such modules in the human cortex; thus, we are considering modules with approximately 300,000 neurons. These circuits are idealizations that were initially proposed and consider the involvement of the dendritic arbor of pyramidal cells (adapted from Douglas and Martin, 1990, 2004.[11,12]

Thus, there is a putative pathway of information processing from the level of cortical modules via pyramidal cells to π-bonds. When resonant frequencies of the cortex are explored, one can see that the electroencephalograph (EEG) describes frequencies of 0-20 Hz in most humans. However, masters of mindfulness practice display persistent gamma frequency (up to 70 Hz), a range that overlaps with microtubular

resonance.[13,14] This may have enhanced capacity for error correction—another aspect of XOR and XNOR, also used to create computer logic gates.

1.3 Relationship of the Logical Algorithm Above to Mathematics (Statistical Tests) and Implications for Interpretation of Statistical Results

The evolution of the infinite series (16th C CEE) in India led to the development of error correction methodology in Indian sciences commencing with the indefinite series (6th C CEE). The purpose of this evolution was attached to measurement (astronomy and navigation) of trigonometric terms and reducing the error. This pinnacle was achieved by accelerating the convergence of infinite series through exceptional terms (a function derived from the practice of indefinite series calculations) [15,16]. In comparison, Catuskoti-like logic is natural to brain function and would permit consideration of exceptions (putative XNOR-type logic in the Right Cortex). This idea of error correction was highly prevalent in India (the logic systems were established with error correction in mind) but was absent in Europe then. This was related to the need for perfect (divine) knowledge and the acceptance that deduction (in the absence of empirical measures, this involved mere metaphysical concepts) is superior to induction (empirical exploration).[3,15]

The advantage of using an accelerated convergence was to derive a sequence of constant terms (within error) in a finite number of iterations. Raju.[3,17] indicates that Newton and Leibniz, developing "the calculus",[18,19] failed to grasp the relatively modest Indian expectation of calculus and instead converted the infinite series into a metaphysical calculation of infinite terms. European statisticians may have independently developed their statistical methods.[15,16] They allied to another deductive (metaphysical) construct, the normal distribution. This is in contrast to Binomial Distribution, which Indians did not use for error correction but to model empirical data for prediction. Adopting gradient descent (differentiation) as an error correction method changed the dependence of machine learning on statistical methods alone. Differentiation applied in computers would be closer to the practice of the Indian Infinite series.[15,16]

Its application in deep neural networks brings error correction with differentiation (infinite series) to science. Machine Learning algorithms also use concepts of probability and statistical techniques for pattern recognition. Introduction of Catuskoti as a logic (a quasi-truth functional logic),[3,20] which has quantum characteristics,[3] as argued in the previous sections, may complete the options of error minimization in machine learning (by marrying appropriate logic with mathematics).

The purpose of adapting matching software algorithms is to interact recursively with XOR and XNOR logic gates with the advent of recent machine learning algorithms. Experiments involving Very Large-Scale Integration (VLSI) chips have been performed in which error correction similar to the cerebral cortex is simulated,[21] The strategy involved transforming a 2-D array of electronic "neurons" into a 1-D array. This hardware is equivalent to Convolutional Neural Networks (CNN). In this paper, we propose a further progression to include recursion between XOR and XNOR logic that would permit unsupervised hypothesis generation and testing.

The Boolean logic is incomplete and difficult to apply to statistical methods within the Machine Learning paradigm. Adopting gradient descent (differentiation) as an error correction method changed this. Differentiation applied in computers is similar to the Indian infinite series (given the limits of int and float data types, any calculation has to be finite, and minute errors will be tolerated.[15,16]

The original suggestion of a recurrent circuit involving a positive feedback loop (involving excitatory output from pyramidal cells in two different layers) modulated by the negative feedback (from GABergic inhibitory input) that leads to a balanced, functional state bears out with subsequent experiments. In this model, the excitatory input from the thalamus would provide the perturbation amplified by the recurrent excitation and passed on as the input to the next layer of cortical modules. Resonant reinforcement of signals with a cortical column (module) is congruent with similar connections through tight junctions of a network of microtubules within adjacent neurons.

We used Catuskoti logic, in which domain expertise in science knowledge is used to demonstrate the micronutrient vitamin D as an essential component in the causation of COVID-19.[22,23] Such knowledge would help design and guide machine learning algorithms to derive more realistic outcomes congruent with empirical science rapidly. This form of unsupervised learning would apply in a completely novel situation where data is sought from an entirely novel set. Published data strongly support that vitamin D supplementation prevents complications and deaths from SARS-CoV-2.[24-27]

2.0 MATERIALS AND METHODS

Here we discuss the following

1) Big data can confirm the previous hypothesis of an inverse relationship between vitamin D concentrations and prognosis in COVID-19.[28]
2) Explore machine learning studies during the pandemic to demonstrate that they were helpful and consider clinically useful algorithms that emerge and demonstrate an example of discovery in a machine learning study
3) We will conduct a thought experiment using the convergence of knowledge about brain function and Machine learning algorithms to suggest paths of development of AI in assisting healthcare

To place the hypothesis under consideration (goal one above), the following empirical facts about vitamin D and immune function will be used.

2.1 Vitamin D Deficiency and Immune Dysfunction—Vulnerability to SARS-CoV-2

There is little vitamin D in the diet. A reasonable quantity of D_2 is present in sun-exposed mushrooms and D_3 in oily fish. Vitamin D is hydroxylated in the liver to 25-hydroxy-cholecalciferol (25OHD; calcifediol). The latter is further hydroxylated to its active molecular form, $1,25(OH)_2D$ (calcitriol), in the kidney and peripheral target cells. One such group of cells is immune cells.

Pre-vitamin D_3 generated in the skin undergoes thermal isomerization to form cholecalciferol (D_3), which is liberated to the bloodstream and is mostly bound to vitamin D binding protein (VDBP). Dietary D_3 and D_2 are absorbed in the intestine, bound to the VDBP, and enter the bloodstream.[29] In contrast, calcifediol is absorbed directly into the circulation from the intestine, bypassing the need for hepatic 25-hydroxylation—hence, it appears within four hours in circulation.[30] Vitamin D takes approximately three days, as it has to go through the lymphatic system and get hydroxylated in the liver to form calcifediol—the precursor for calcitriol.[31]

2.1 Vitamin D and Functions of the Immune System

Seventy-five percent of the immune system functions dependent on having sufficient vitamin D in the bloodstream on.[24,32,33] deficiency-increase vulnerability to diseases, especially infections.[34,35] like SARS-CoV-2.[1,36] When the circulating concentration of calcitriol is insufficient to enter immune cells like macrophages.[24,37] adequate concentrations of the precursor calcifediol could be achieved in emergencies.[30,33]

2.2 Vitamin D-enhance the Expression of Anti-microbial Peptides (biomarkers)

Vitamin D has broader and complementary biological and physiological functions in the human immune system.[38,40] It stimulates both innate and adaptive immune systems. Besides stimulating immune cells, vitamin D adequacy is essential for neutralizing antibodies,[41] producing and coordinating anti-microbial peptides,[42,43] and angiotensin-converting enzyme-2 (ACE-2).[44,45] for chaperoning and neutralizing circulating pathogens.[46]

Procalcitonin, beta defensin-2, and human cathelicidin (LL-37) are three examples of measurable biomarkers in circulation that significantly reduce infections/sepsis, including COVID-19.[47-49] These can be used as guidance to assess the severity and predict potential complications. Beta-defensin and cathelicidin molecules are highly effective against invading bacteria, fungi, and viruses.[48,49] Higher infection/sepsis and complications are associated with lower circulatory concentrations of beta-defensin-2.[47] SARS-CoV-2-associated down-regulation of defensins increases the risk of complications from SARS-CoV-2.[47]

In these circumstances, administering vitamin D increases the expression of anti-microbial genes and the secretion of peptides from macrophages (beta-defensin 2/defensin-beta4 (HBD2/DEFB4) and cathelicidin that have a major controlling effect on pathogens.[49,50] These anti-microbial proteins/peptides suppress cytokines and the risk of storms and inflammatory processes by COVID-19, inhibit the replication of viruses and promote chaperoning and elimination of viruses from cells by autophagy and circulation.[50]

2.3 The Serum 25(OH)D Concentration Needed for Optimal Immune Cell Responses

The serum 25(OH)D concentration required to provide sufficient intracellular concentration for autocrine activity is about 50 ng/mL (125 nmol/L).[24,33] The average range of circulating 25(OH)D in populations living in the open appears to be 40-60 ng/mL (100-150 nmol/L).[51-53] Unlike calcifediol [25(OH)D], circulating calcitriol [$1,25(OH)_2D$] is too low and, thus, is not taken up by peripheral target cells such as macrophages.[30] Calcitriol needs to be synthesized at higher concentrations—about 20 times than in circulation for autocrine and paracrine functions of immune cells.[33] Thus, to achieve such concentrations of calcifediol in emergencies and acute treatment, it is necessary to administer the correct doses of calcifediol, not calcitriol.[30,33]

Another path in which vitamin D deficiency leads explicitly to vulnerability to COVID-19 is via its impact on the renin-angiotensin system (RAS). Vitamin D deficiency has two key effects on this system; firstly, it inhibits the rate-limiting step of synthesis of RAS, the renin. Further, vitamin D deficiency also decreases tissue and circulating angiotensin-converting enzyme II (ACE-2). ACE-2 converts angiotensin II to the vasodilator peptide $Ang_{(1-7)}$. Thus, hypovitaminosis causes a systemic increase in angiotensin-II, leading to, among others, vasoconstriction and stimulation of inflammatory cytokines, increasing the risks for cytokine storms.[54,55]

Non-genomic actions of calcitriol include the hormonal activities of and modulation of the immune system. Calcitriol converts T helper cell 1 (Th1) to T helper cell 2 (Th2), transforming these cells from pro-inflammatory to anti-inflammatory status. Intracellular low calcitriol concentrations result in TH1 and Th17 cell-mediated excess inflammatory response in vulnerable persons that could lead to cytokine storms and ARDS, as in COVID-19.[56,57] Additionally, both metabolites of vitamin D_3, calcifediol, and calcitriol strengthen epithelial and endothelial barriers against fluid leakage and infections.[58,59]

In addition, low circulating D_3 and calcifediol molecules cause endothelial cell dysfunction,[60] and impairment of

their gap junctions; these abnormalities increase the risk of thrombus formation and embolism, fluid leakage,[61] and virus escaping into soft tissues. In addition, excess angiotensin-II-mediated intense vasoconstriction reduces immune cells' access to affected tissues, impairs membrane-bound ACE-2 actions, and enhances the adverse effects of SARS-CoV-2 on its production. Collectively, these facilitate the development of cytokine storms. Moreover, these cascades of events contribute to ARDS and thrombo-embolism, which are the principal causes of mortality in COVID-19.

3.0 RESULTS—Clinical and Epidemiological Evidence for the relationship between Vitamin D and COVID-19 (Large datasets and meta-analyses)

Having used the Nalanda paradigm to demonstrate that there was sufficient evidence in 2020 to recommend vitamin D boosting as a public health measure,[22-27] we would like to expand this evidence base further. Firstly, we will critically review the largest vitamin D and COVID-19 meta-analysis.

3.1 Vdmeta.com—(now called c19early.org/dmeta.html)

The c19early.org/dmeta.html has analyzed studies involving a population of approximately 350,000 subjects. Since these are real-time analyses, the number will continue to increase with new data. The authors of this site, the largest meta-analysis on vitamin D levels and COVID-19 outcomes, analyzed 141 naturalistic studies and 100 treatment studies using standard meta-analytic tools when preparing this paper. We opted to use a random sample of 10 papers on this site to provide a descriptive perspective of the papers, which could be generalized to the population of articles illustrated on the site.

We randomly selected ten papers from the 138 listed on (vdmeta.com/ https://c19early.org/dmeta.html) as of October 2022,[62] After subjecting integers from 1 to 138 to randomization, the first line of 10 numbers was derived, representing the papers sequentially listed on vdmeta.com (c19early.org/dmeta.html). We constructed a measurement of the level of quality on a 3-point scale (low=1, medium=2, high=3) for statistical methods, using vitamin D sampling methods to measure the quality of the papers that are of specific interest to us (see below).

3.2 Study Quality—The study quality was classified according to the following scheme

The timing of the Vitamin D sample (validity of measurement) and vitamin D level (ideal 50ng/mL or above) were considered important features for valid outcomes (other study design features are described in Table 3). Even though we disagree that retrospective should not be a measure of inadequate quality, we nevertheless went with the convention of penalizing this even though the study of Israel et al., which has a superior design with stratified vitamin D levels (but they considered deficiency as levels below 12 ng/mL). The design was otherwise superior; the design was assigned 2/3.

a) Vitamin D sampling

✓ Within one year prior to admission >40 ng/mL or continuous measure, prospective–3

✓ Admission only (reverse causation) but clear group separation of vitamin D levels, retrospective–2

✓ Levels taken >one year from presentation, > 20 ng/mL considered sufficient–1

b) Statistical method (see discussion later for critical rejection of regression); if too many variables were analyzed to ensure evident power, inadequate power was assumed; use of regression did not penalize if group comparisons or other reliable statistics (e.g., propensity score) was used:

- Group comparison + adequate power—3
- Regression + adequate power—2
- Regression only + inadequate power—1

A related summary of data is illustrated in Table 3. The scores of quality for each paper are found in the last column.

Table 3: Ten clinical studies were selected randomly. These studies uniformly accepted a lower vitamin D adequacy standard than the basic science evidence indicated. The quality of the studies had a median of 4.5 and a mode of 5. During scrutinization, we discovered an error in selecting some of the papers based on randomization (selecting one paper above the ordinal list as indicated. These six papers are compared to those that should have entered the Supplement 1- erratum analysis. We found no substantial difference in the quality of the papers. This further supports that the generalization to the total data set is valid. More details are [presented in the Supplement 1, after references.

Paper	Design	Infection	Hospitalization	Death	Statistics	Significance/ Effect Size
Hastie et al. (2020) [63] UK.	UK Biobank data Retrospective Obesity, diabetes, hypertension controlled N= 449	NA	NA	NA	Regression	Correlations were insignificant, probably due to the inappropriate impact of colinear effects being removed. Quality = 3
Szeto et al. (2021) [64] US	All hospitalized patients Retrospective Cohort Study Information about medical treatments unavailable N= 700 (actual number N=93)		Negative Correlation with vitamin D level		Comparison of means (Chi^2, Wilcoxon rank sum) Multivariable logistic and linear regression	The non-significant difference in 21 variables Probable insufficient power Quality = 3
Ozturk et al. (2022) [65] Turkey	Vitamin D level and inflammatory markers Retrospective N= 300; three groups severity controlled. Probable inadequate design (The difference in deficiency level was not detected)	NA	Severity Mild Moderate Severe (in an experimental design to test vitamin D level, severity should have been a dependent variable)	0% 0% 18.7%	Comparison of groups Multivariate Logistic Regression	Deficiency 60.8% 62.1% 76.3% non-significnat No correlation between vitamin D 25 variables Probable insufficient power Quality = 3
Bogliolo et al. (2022, study period 2020) [66,67] Italy	Prospective observational study 25(OH) D level Hospitalized N= 361	NA	Inpatients	Increased correlation with deficiency (< 20 ng/mL)	Cox Model Propensity and survival analysis	Mortality correlation Non-significant Hazard Ratio = 1.18 Quality = 4
Dana et al. (2022) [68] Iran	Inpatients Diabetes Mellitus and Gender as independent confounders N= 831		Severity Should have been a dependent variable in the study	The odds of death of older females and people with diabetes are greater with vitamin D deficiency	Logistic Regression	A significant hazard ratio of older females and Diabetics Probable lack of power and design fault missing detection of a stratified difference in death rate (potential OR of 1.8- see text) Quality = 3

Israel et al. (2022) [69] Israel	Matched Hospitalised (N= 2533) and Non-Hospitalized (2533)PCR positive compared with each other and PCR positive (N= 41757) compared with non-PCR (417,570) Longitudinal vitamin D levels assessed	Community	Inpatients	NA	Fisher Exact, Wilcoxon Mann-Whitney U, Logistic Regression (< 12 ng/mL is considered a deficient level)	Significant inverse correlation between vitamin D level and infection, as well as the severity OR between 1.2 – 1.5 Quality = 5
Jain et al. (2020) [70] India	Prospective observational (case-control) study Control = 91 Cases (ICU)= 63 Confounders not considered Demographic differences between the groups	NA	ICU vs. other inpatients	NA.	Correlation between vitamin D level and inflammatory markers	Highly significant: The difference in vitamin D levels ICU group uniformly vitamin D deficient (97-98%) OR ~ 3.2 Quality = 5
Sanchez-Zuno et al. (2021) [71,72] Mexico	Randomised Controlled study (not double-blind) Outpatients N=42 Cases received 10000 IU vitamin D for two weeks Supplemented group = 22	NA	NA	NA	Group comparisons Chi^2 , Fisher's exact, Mann-Whitney U, Spearman Wilcoxon Rank Sum, Logistic Regression	Significant difference on days 7 and 14 Supplemented patients with > 3 symptoms = 0 Non-supplemented patients with > 3 symptoms = 20% At Baseline OR ~ 1.35 for the difference between sufficient and insufficient patients for symptoms > 3 Quality = 5
Junior et al. (2022) [73] Brazil	Inpatient study Vitamin D level as part of a broader study Prospective Cohort design Highly educated Elderly Population N= 201	NA	Severity (including a requirement for mechanical ventilation)	NA.	Chi^2 ANOVA Logistic Regression	Vitamin D level < 40ng/mL Predicted respiratory failure Quality = 5

*Smaha et al. (2022) [74] Slovakia	Cohort study All patients treated with cholecalciferol (30000 IU for three days followed by 7500 IU/day) N= 357 Vitamin D level on admission	NA			Multivariate Logistic Regression	80% had <30ng/mL vitamin D level The vitamin D level is independently associated with mortality, with < 12 ng/mL particularly associated. Quality = 5
*[Note: c19early.org/dmeta.html incorrectly names Smaha et al. as Juraj et al.]. Please see Supplement 1.						

Even though all studies appear to accept a lower minimum standard of 30 ng/mL as vitamin D sufficiency (the rationale for requiring vitamin D levels above 50 ng/mL[24,33] was discussed earlier), the study designs were adequate (all were assigned 2/3 except Hastie et al. assigned 1/3). The following statistics summarise the characteristics of the sample of studies we assessed:

Inpatient studies were 70%, indicating the degree of control that could be applied, considering the difficulties during an emergency. There were 20% prospective and 10% randomized control studies (RCTs). Quality of design and statistics averaged 4.1 with a Mode of 5 (good quality). On further elaboration, 10% were medium quality, 50% were medium to high, and 40% were low to medium quality. Large studies (as n >5000) comprised 10% of the population of studies and would add validity. Given this randomized sample of studies, we infer that these findings could be generalized to the studies within the c19early.org/dmeta.html site.[62]

Considering some bias, the overall effect size for the 138 studies is a 55% improvement ($Tau^2 = 0.26$, $t^2 = 85.8\%$ with $p < 0.0001$). Thus, even though studies are not all of a similar high standard, there is a high effect size, and the overall result is significant. While one negative study in the eight studies above was well-designed, we found major design flaws in all other negative studies listed on vdmeta.com (now changed to c19early.org/ dmeta.html).[75] As of writing, the site lists 106 treatments and 149 sufficiency studies. Of the treatment studies, 24 are RCTs. The outcome is similar whether RCT or the general treatment groups were used (36% vs. 37% improvement).

3.3 Specific Design and Statistical Faults (examples)

Concerning design faults, we found that using severity instead of vitamin D level as an independent variable may bias the outcome. This could be illustrated in the study by Dana et al., in which we changed the data display in Table 4 as follows:

Table 4: Relationship of severity and vitamin D levels (reproduced from Dana et al., 2022[68]).

	Very severe deficiency	Severe deficiency	Insufficiency	Sufficiency
Total	46	197	206	376
Hospital	23 (50%)	73 (37%)	93 (45%)	159 (42.3%)
Severe	7 (15.2%)	35 (17.8%)	41 (19.9%)	59 (15.7%)
Dead	8 (17.4%)	30 (15.2%)	18 (8.7%)	49 (13%)

Observing the table demonstrates a precise gradation in the death rate if we compare the insufficient group with the deficient group (OR ~ 1.8). Subjects with sufficient levels should neither be included in RCTs nor statistics. Those presenting to hospitals are self-selected groups, most vulnerable to infection. This group may not necessarily have vitamin D deficiency but may be vulnerable for other reasons.

Another design fault concerns the choice of multiple regression as a statistic without considering the impact of multi-collinearity of related comorbidities—these dilute the impact of vitamin D. This was particularly evident in the study by Hastie et al. A good example of using multivariable regression without dropping important confounders is the big data study by Kaufman et al., in which regression was used in a stratified design to examine proxies for skin color and sun exposure.

Raisi-Estabragh et al.[76] paper used multi-collinearity that would have diluted the contribution from the vitamin D level, as we suggested above. In designing studies using regression analysis, confounders opposing the experimental hypothesis should have been excluded, and colinear variables contributing to the index variable should not be used, as they also dilute the index variable. This issue could affect some Machine Learning paradigms. A further persistent problem with the studies of the UK Biobank data is that the vitamin D levels were measured over 20 years prior to the studies (but were too remote). Even though the latter study was better designed, the results are invalidated due to this problem and the problems with regression.

Finally, the variance Inflation Factor[77] rules out one of two highly correlated factors from a regression equation. However, the usual cut-off of VIF is between 4 and 10.

Raisi-Estabargh et al. used a VIF cut-off of 2.5, meaning that moderate correlation: e.g., ethnicity and vitamin D level with R^2 of 0.6 would require excluding one from the regression equation)[76] Thus, running multivariable regression on COVID status as the dependent variable would tend to minimize the impact of vitamin D due to the presence of ethnicity and age in the model used to test the contribution of vitamin D levels. The reasoning behind the decision of Raisi-Estabargh et al. is unclear.[76]

4.0 Big Data Studies

Two studies have accessed large databases (big data) regarding vitamin D and COVID-19 in the United States.[28] The first was published in 2020.[78] and accessed the National Clinical Laboratory data; the second[79] was published in 2022 and accessed Veterans Administration Corporate Data Warehouse (CDW) electronic health records. First, Kaufman et al.,[78] using data from a sample of 191,779, answered three broad questions:

1) The relationship of SARS-CoV-2 positive rate to 25(OH)D concentrations: There was a doubling of the infection rate between 50 ng/mL (125 nmol/L) and 20 ng/mL (50 nmol/L) (figure 6 demonstrates the second-order polynomial curve that best fits the data). (Figure 2).
2) The relationship between three latitudes and ethnicity (Black, Hispanic, and White) was tested. There was a gradation of the odds ratio of a positive test from the lowest to the highest latitude and from control—predominantly White neighborhoods to Hispanic to black. The difference in odds ratio is 2.03 for Black neighborhoods and 2.66 for northern most latitudes. These tests reflect and evaluate the level of sunlight exposure and the ability of the skin to produce cholecalciferol (D_3) with such low sun exposure.
3) There was also a comparison according to gender and age. Males had an increased odds ratio of 1.24, while the odds ratio for those above 60 was only 0.84. This is contrary to the common opinion of the opposite. It indicated that a considerable proportion of the younger population has significantly low vitamin D and potentially higher susceptibility to the SARS-CoV-2 virus. However, it is unclear whether this reflects a higher proportion of the older white population compared to a younger population with darker skin ethnic groups.

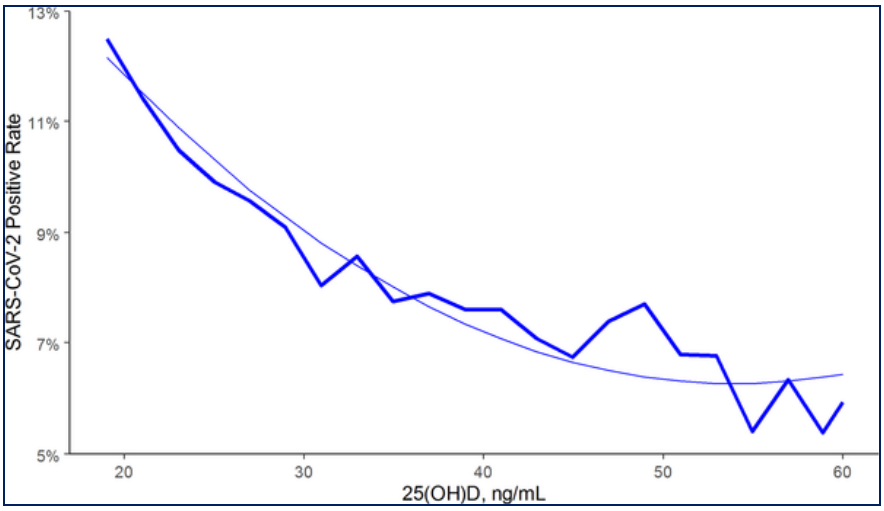

Figure 2: The second-order polynomial curve fitting the data in Kaufman et al. Big Data study. It illustrates the relationship between serum 25-hydroxyvitamin D [25(OH)D] concentrations and the rate of SARS-CoV-2–positivity in a large sample (n= 191,779) from the USA (weighted second-order polynomial regression fit to the data). The smooth line is a second-order polynomial fitting the data: (unadjusted odds ratio = 0.979 per 1-ng/mL increment, 95% confidence interval, 0.977–0.980) [reproduced with modifications from Kaufman et al.[78]

The VA study used the propensity matching technique to match groups statistically. The index and control groups were 33,000 each for vitamin D_2 supplementation and 199,000 each for vitamin D_3 supplementation from an overall population of veterans of around 650,000. A summary of the essential conclusions of this study:

1) Vitamin D_3 and D_2 supplementation effectively reduced COVID-19 symptoms by 28% and 20%, respectively.
2) Vitamin D_3 and D_2 supplementation reduced mortality by 33% and 25%, respectively.
3) Veterans receiving higher doses of supplements obtained greater benefits than those with lower doses.
4) Those with vitamin D blood levels between 0-19 ng/mL achieved the most significant benefit from supplements.

Veterans with Black ethnicity had more significant COVID-19 risk reduction than white veterans. The findings further confirm what the large meta-analysis reported above. These two US studies together confirm

that low vitamin D—levels or lack of supplementation—are associated with a higher risk of acquisition of COVID-19 and its severe outcomes (particularly mortality).

A serum level of 50 ng/mL would be associated with minimizing the risks of infection. This was confirmed, supporting our hypothesis that such a level is necessary to provide the intracellular concentrations in immune cells to generate robust immune systems [61,80-82]. The effect sizes provided in these large studies are congruent with what was evident in mid-2020.

5.0 Machine Learning Models Applied During the Pandemic

Below, we review and analyze two selected papers that describe machine learning algorithms used during the pandemic. The first is a review of deep learning methods, while the second is a specific study of predicting outcomes. Ashraf et al.[83] reviewed neural network (deep learning) models utilized throughout the pandemic and identified five broad areas in medicine in which deep learning had been applied. These areas were,

1) Medical imaging (studies used CNN, LSTM, ResNet)
2) Disease Tracking (studies used LSTM, GRU)
3) Protein structure prediction (use of ResNet)
4) Drug Discovery (use of GAN)
5) Virus severity and infectivity (study using CNN, LSTM, and GWPA, the latter being an imaging methodology for genomes)

The neural network models outlined above are Convoluted Neural Networks (CNN), Long Short Term Memory (LSTM), Residual Networks (ResNet), Gated Recurrent Units (GRU), and Generative Adversarial Networks (GAN). The studies investigating disease prognosis achieved an accuracy of less than 95%—notable tasks involved feature extraction in making a COVID-19 diagnosis and distinguishing COVID-19 pneumonia from other forms.

Stryzynski et al.[84] used machine learning in hospitalized patients to predict prognosis before positive PCR based on standard lab tests and using non-neural Network algorithms (e.g., Logistic Regression, K-nearest neighbor, random forest, AdaBoost classifier, bagging classifier, gradient boosting classifier). Applying several classifiers of which gradient boosting classifier was most accurate, they found that procalcitonin (PCT) level and complete blood examination provided sufficient predictive power to identify those who would become COVID-19 positive. Additionally, older patients with higher PCT, Troponin, CRP, and lower hemoglobin and platelet/neutrophil ratios had a poor mortality prognosis. Despite the classifiers having a mean accuracy of only 0.76, combining different tests provided sufficient predictive power for the above results.

While such a breakdown of parameters may not appear particularly helpful in considering specific treatment strategies to improve prognosis, it should be kept in mind that such evidence early in hospitalization would permit more aggressive early therapy. Procalcitonin (precursor of calcitonin), a biomarker molecule,[85,86] is known to be inversely proportional to survival and vitamin D level on admission to the hospital.[85,87,88] Treatment with a high dose of vitamin D reduces, and procalcitonin increases survival.[87,88] Serendipitously, Stryzynski et al.[84] have inadvertently included a proxy for vitamin D (procalcitonin) levels in their analysis and demonstrated its validity (Figure 3).

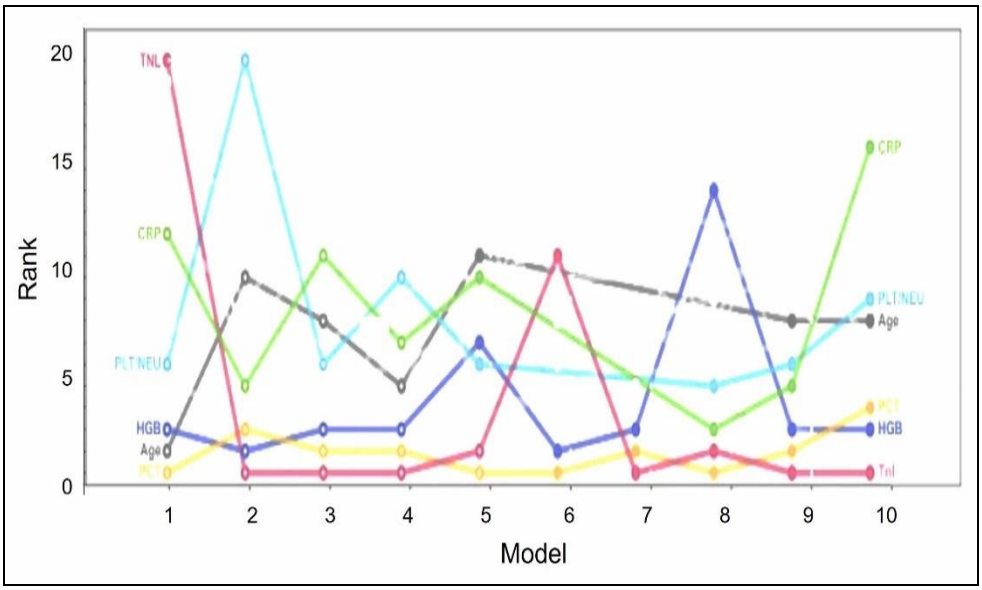

Figure 3: Survival analysis with cross-validation—ranking of six clinical laboratory markers that were consistently scored high in different models by the classifier models. PCT (procalcitonin) ranked the highest. TNL (troponin) has a more variable classification but trends toward the top (reproduced with permission – Styrzynski et al.[84]).

Using ten classifiers, they ranked how well they classified each lab datum: procalcitonin (PCT) consistently in the top three crucial features except for the lowest-ranked classifier in which Troponin (TNL) is classified as number one, as a marker of prognosis. However, the latter is not as consistently classified. Gradient Boosting had the most accuracy of the classifiers, and the mean test accuracy was 0.76. Figure 4 illustrates the feature importance of various laboratory tests and demonstrates the importance of procalcitonin (PCT) as an example of predicting prognosis.

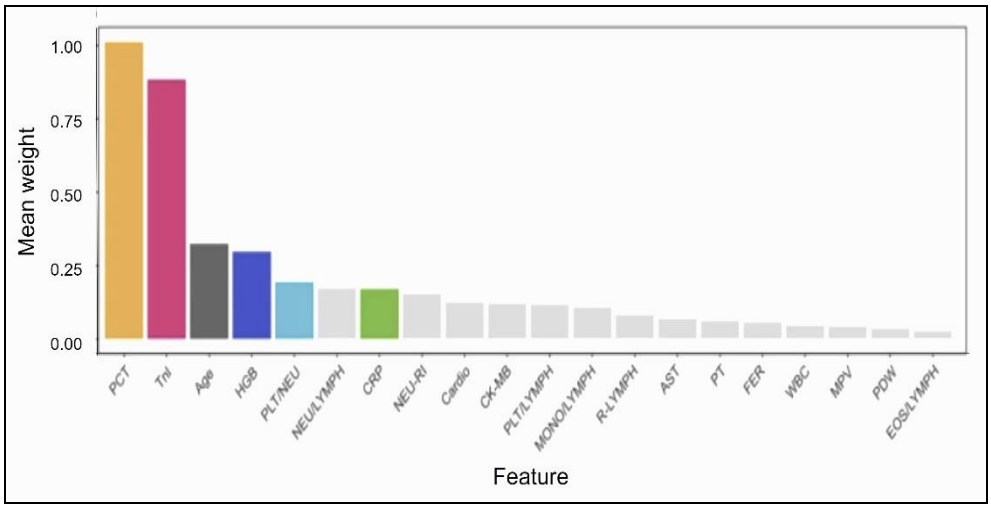

Figure 4: The bar graph of features important for different laboratory biomarker molecules and clinical markers displays data from Figure 3 with better clarity. The mean weights of various elements assessed in permutations analysis confirm the importance of illustrated features in distinguishing deceased and surviving from SARS-CoV-2 positive patients (reproduced with permission Styrzynski et al.[84]).

5.1 Suggested Machine Learning Algorithms for Vitamin D/COVID 19 Big Data Sets—A thought experiment

The study of Kaufman et al.[78] was limited to laboratory data but was nevertheless a valuable paper early in the pandemic. Gibbons et al.[79] used many veterans' clinical records to analyze the relationship of vitamin D to COVID-19 and its prognosis. The former paper is useful mainly as a source of past vitamin D data to correlate with proxy for vitamin D concentrations. If laboratory data in the latter paper also included acute prognostic tests (such as procalcitonin discovered by Styrinski), this would be an invaluable source to validate a machine learning AI model in the following thought experiment.[28]

However, machine learning paradigms, such as a network model, may demonstrate the central position of vitamin D levels concerning skin color, latitude, age, and gender and its strong correlation with COVID-19 positivity. While the number of features in the study of Kaufman et al. was limited, running a decision tree model with feature importance would be interesting to determine if vitamin D level is more important and central than the other measures (age, ethnicity, latitude). In this thought experiment, we would consider a generative process to develop the feature importance.

Gibbons et al.[79] had data that could include essential confounders. It is, therefore, a critical data set that could apply a machine learning paradigm, particularly concerning the utility of PCT (as a marker of low immunity and vitamin D level). If so, then testing of PCT level among other tests on admission and any patient presenting with symptoms would be a prognostic indicator and a pointer to treatment (in this case, specifically vitamin D_3 or calcifediol). We expect that the appropriate machine-learning model could emulate these deductions reached by the human mind. We propose using an FPGA array to emulate a recurrent network between an XOR and an XNOR circuit and to develop a generative machine-learning algorithm to exploit the network described below (Figure 5).

We have noted that complementary logic could operate between the hemispheres. Such logic could be extended to the neuronal level. XOR-type logic has already been demonstrated in the dendritic arbor.[89] There is also evidence that synaptic learning occurs only, if both pre- and post-synaptic thresholds are met in NMDA junctions (i.e., this would be both A and not A logic in Catuskoti).[90] Recurrent circuits in the dendritic arbor involve back propagations that theoretically indicate possible interaction between these logical membrane potentials.[91]

Given the similarities between natural and artificial neural networks and complementarity seen in the logic of information processing at various levels of the nervous system, the most parsimonious explanation for such widespread complementarity is to hypothesize that the simplest logical model would be recurrence between

XOR and XNOR type gates throughout the nervous system. This would be particularly applicable to hemispheric differences. Thus, we propose to take this hypothesis to extend machine learning to develop the capacity to generate novel hypotheses.

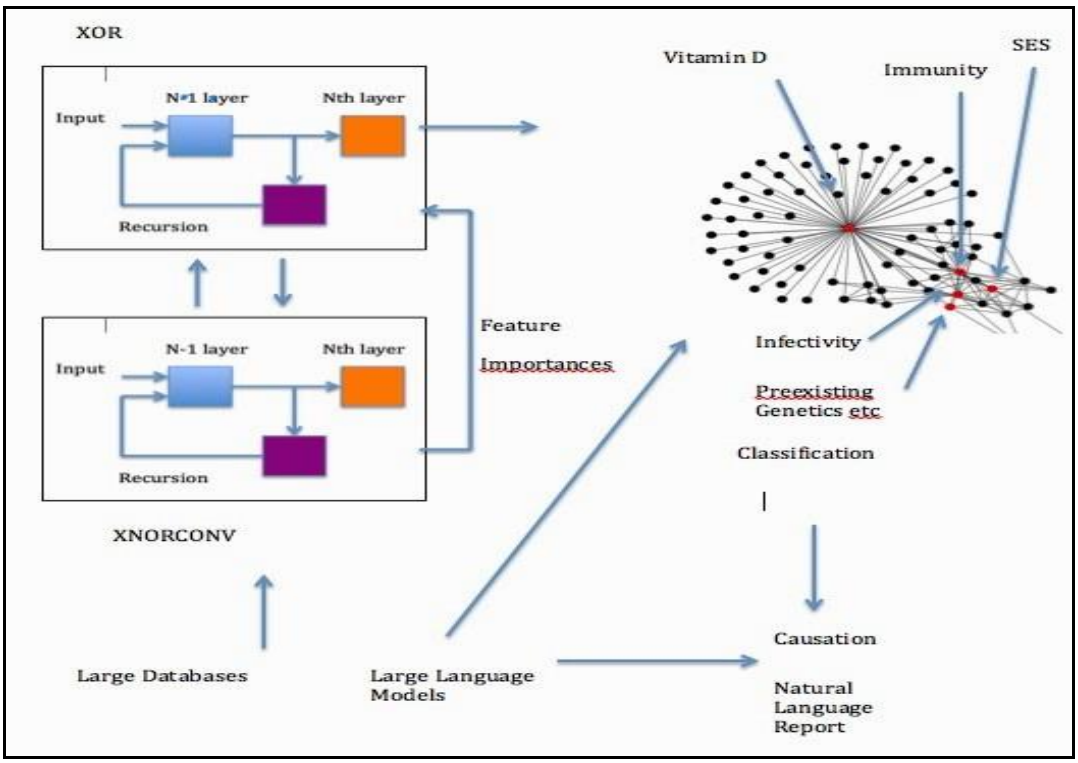

Figure 5: In this thought experiment, data during the COVID-19 pandemic were accessed from an extensive database and/or through a literature search and collated using statistical techniques—normalization. The arrows indicate the relationships between various components. Recursion could occur both within the XOR and XNOR modules and between them. After data is received by the XNORCONV system Field Programmable Gate Array (FPGA), a set of essential features are identified (Hypothesis Generation) and passed on to the XOR system (FPGA). Here, XORing would match other features to the most crucial ones (vitamin D).

If sufficient correlations exist, such features will be classified under vitamin D (Hypothesis Testing) as the common denominator. Next, information from Large Language models would generate a causation hypothesis. The causation hypotheses would be subject to temporal priority (e.g., using time series data and Markov processes). Further, the confounder of causation and reverse causation will be statistically analyzed. Finally, a Large Language Model (LLM) will generate a report (example below).

5.2 Example output

The literature search and a large database found the following significant risk factors as principal vulnerabilities for COVID-19. These include genetic factors, socioeconomic factors, pre-existing immune compromise, vitamin D, obesity, age, skin color/ethnicity, season, latitude, and chronic diseases like diabetes, hypertension, and heart disease. Vitamin D deficiency is considered the final common pathway related to obesity, old age, skin color, season, latitude, and diabetes. Besides, several acute lab results could predict prognosis (procalcitonin, beta-defensin, cathelicidin). Precisely, procalcitonin could predict vulnerability due to significant vitamin D deficiency, indicating immediate treatment with calcifediol (note: this is a fictitious output from a putative Large Language Model)'.

In the emulated FPGA network, the XOR circuit will attempt to generate hypotheses about live data (e.g., of an established hypothesis about vitamin D level and prognosis of COVID-19). An XNOR circuit (XNORConv) will generate feature importances (e.g., using either or both big data sets).[28] A network model generated using the XOR circuit and relevant code would demonstrate important relations between features, leading to the classification of vitamin D as an essential feature representative of some factors. There may even be a place for Large Language Model (LLM) methods, such as Retrieval Augmented Generation (RAG), in the classification process.

The classification would be followed by a causation hypothesis (methods for time series such as the Markov chain could be applied here) to generate the desired hypothesis. Whether the machine model could generate the hypotheses already generated by humans would be a

test of its validity. The present data supporting the hypothesis about vitamin D and COVID-19 vulnerability would constitute a good training data set (see the example output from the putative machine learning model as depicted in Figure 5).

It should also be noted that methods using XOR and XNOR logic already increase the speed of machine learning algorithms. We conjecture that combining these methods in mobile platforms will permit the use of LLMs in the field and generate live data that is useful for health practitioners.

6.0 DISCUSSION

We have discussed logic, its relationship to statistics and data science, and brain function. Considering their relationship, we have drawn an analogy between brain function and current neural network paradigms and outlined the potential for further cross-fertilization of knowledge in each field. Catuskoti logic can be related to both quantum logic and the function of the mammalian cortex and could serve as a template to expand the current deep learning model. This could be achieved by converting it to an iteration between XOR and XNOR logic gates, providing flexibility and speed and developing the capacity to generate hypotheses and reasoning.

We demonstrated the hypothesis that vitamin D deficiency leads to impaired immunity and other impairments, which cause serious vulnerability to outcomes of COVID-19. Therefore, we suggest that this proven hypothesis can be used to generate hypothesis-testing machine learning algorithms. The utility of such algorithms could include future use in emergencies, predicting prognosis, and rapidly evaluating the efficacies of treatments.

In emergencies, automated deep learning techniques for generating hypotheses could greatly facilitate the rapid deployment of tests of such hypotheses using large data sets, making them less vulnerable to political manipulation. Notebooks of code (e.g., python code) and FPGA code could be easily shared and utilized rapidly worldwide.

Based on published data, we suggest that calcifediol should be included in the treatment armamentarium for early treatment of COVID-19. Suppose a machine learning model proposed in the thought experiment above had been available. In that case, it is likely that in conjunction with appropriate lab tests (e.g., procalcitonin), such early treatment would have been deployed during the pandemic.

7.0 CONCLUSIONS

Catuskoti should be used in mathematical frameworks with machine learning and quantum logic to capture broader medical data sets and faster decision-making in policies and drug approvals. Using such could have permitted proper decision-making by regulators and health authorities and prevented the gridlock during the COVID-19 pandemic. Applying machine learning paradigms to medical decision-making would reinforce the machine learning process, leverage early identification, and use early treatments already approved by regulators. We have theorized that developing novel neural network methods with non-Boolean logic, namely quantum Catuskoti logic, facilitates proper coding algorithms and logic gates. Such an approach could provide rapid analysis of extensive data in an emergency using machine learning in the future.

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Data availability: Supplement 1 (see below) describes the data extraction method. Datasets generated and analyzed during the current study are available from the author, AKP, upon reasonable request.

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Supplement 1:
Modifications to Randomization used in Table 1

Randomization—comparison of two groups—one group differing from the other by being adjacent to the random group by 1.

During the proof-reading phase of this paper, we discovered that 6 of the papers were selected by error due to miscounting of their ordinal position on the list of papers in http://c19early.org/dmeta.html by incrementing 1 to the actual position of each paper at and beyond 70. Due to this, we felt it was important to analyze if the original conclusion about the quality of papers at the site is still valid.

Accordingly, we compared this group with the papers that should have been randomly assigned. The table below displays the main concerns of our analysis, which was to consider if vitamin D sampling is sufficiently valid and if statistical methods beyond regression and correlation were used (e.g., between-group statistics). The quality of the random group is better in terms of median quality, but the mode remains the same. Also, the total sample number for the random group is smaller, which may pose issues of significance or power. In both groups, there were two Retrospective Observational studies (Ret.Obs), two Cohort studies, and one cross-sectional (Cross), each and one RCT (see Table s1).

There is also a degree of subjectiveness used to rate the quality. For example, the Bogliolo paper was strictly classified with a quality of 4, although it may be argued that it is at a level above this (they used propensity scores). This change alone would have raised the median to five, making it identical to the random group. Nevertheless, we maintain the original classification as decided after constructing the standard.

Besides, as we found a statistical error in Dana et al., an RCT procedural error in Cannata-Andia et al. was also seen. The two studies used 100,000 IU bolus doses of vitamin D for treatment of the index group after hospital admission, and this resulted in only an increase of serum 25(OH)D from 17 ng/mL to 29 ng/mL in the latter. The higher level would have required several days (generally, three to four days) to achieve and would have been insufficient to prevent severe symptoms or complications. Nevertheless, the authors reported significantly fewer ICU admissions in subjects with the highest calcidiol levels. The failure of this paper is in line with what we anticipate in the biological diathesis postulated in the text.

Thus, the groups are primarily comparable in quality and type, and the differences do not qualitatively or quantitatively affect the conclusions on the likely representativeness of the overall sample of papers at http://c19early.org/dmeta.html.

The procedure for randomization with the seed is illustrated in Figure s2, and a description of the error by 1 integer is given in the paper selection. Nevertheless, we proposed that the randomization directly influenced this, and the only result appears to have been a form of stratified randomization.

Table 1: Supplement 1

First Group - Random +1	Quality (sampling + stats)	N / study type	Random Group	Quality	Number (N)/ Study type
Sanchez_Zuno et al,[1]	2+3	42/ RCT	Pimental et al.,[2]	2+3	25/ Cross
Bogliolo et al.,[3]	2+2	361/ RetObs	Charla et al.,[4]	2+3	178/ RetObs
Junior et al.,[5]	2+3	201/ Cohort	Cannata-Andia et al[6]	2+3	543/ RCT
Dana et al.,[7]	2+1	831/ Cross	Zeidan et al.[8]	2+3	94/ Cohort
Ozturk et al.,[9]	2+1	300/ RetObs	Baykal et al	2+2	75/ RetObs
*Smaha et al.,[10]	2+3	357/ Cohort	Saponaro et al.,[11]	2+3	92/ Cohort
Total	-	2092	-		1007
Median	4.5	-	-	5	-
***** Smaha et al. is identified by Smaha's first name on the website and occurs as Juraj et al., above Saporano et al.					

Figure Supplement 1 illustrates the randomization procedure and the resultant matrix from which the first 10 random numbers were chosen (first line).

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Read this way ----->
71 133 114 138 129 110 13 10 35 29
111 69 88 61 93 103 33 109 106 85
117 53 78 50 102 132 26 116 23 7
1 37 128 3 105 32 19 48 74 25
22 58 30 51 67 8 79 104 75 20
55 107 97 39 94 108 125 121 5 14
115 15 9 72 98 57 24 31 68 89
6 124 99 136 82 70 49 21 131 120
80 130 46 87 95 135 92 44 4 100
42 38 47 28 18 119 65 122 62 52
134 118 112 83 84 77 63 34 2 16
86 17 41 59 43 81 66 96 40 91
73 113 45 137 101 36 27 60 127 12
90 54 64 123 11 126 56 76
```

Figure 1: Suppement 1

Randomization was done on the website
http://www.jerrydallal.com/random/random_permutation.htm
using integer range 1 to 138 (number of papers on the list in October 2022) and the seed 123.

Procedure: The random numbers 71 to 138 were assigned by mistake to the paper one ordinal level above (e.g., 71 was assigned to the 70th paper due to a counting error at some point before this). The website has maintained its list of papers according to temporal priority to be listed on the site (a comparison of the site trawled by the Wayback machine of the Internet Archive confirms that the list has remained pristine). This made it possible to recover the papers that should have been assigned. It could be argued that random status was not seriously affected as these papers were just one before the actual random papers, thus still chosen by the random process (a sort of stratified randomization).

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