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REVIEW ARTICLE

Artificial Intelligence to Predict Chronic Kidney Disease Progression to Kidney Failure: A Narrative Review

Zane A. Miller[1,2] | Karen Dwyer[1,3]

[1]Faculty of Medicine, Dentistry & Health Sciences Melbourne, The University of Melbourne, Melbourne, Victoria, Australia | [2]Epworth HealthCare Medicine, Richmond, Victoria, Australia | [3]The Royal Melbourne Hospital Nephrology, Parkville, Victoria, Australia

Correspondence: Zane A. Miller (zanemiller711@gmail.com)

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ABSTRACT

Chronic kidney disease is characterised by the progressive loss of kidney function. However, predicting who will progress to kidney failure is difficult. Artificial Intelligence, including Machine Learning, shows promise in this area. This narrative review highlights the most common and important variables used in machine learning models to predict progressive chronic kidney disease. Ovid Medline and EMBASE were searched in August 2023 with keywords relating to 'chronic kidney disease', 'machine learning', and 'end-stage renal disease'. Studies were assessed against inclusion and exclusion criteria and excluded if variables inputted into machine learning models were not discussed. Data extraction focused on specific variables inputted into the machine learning models. After screening of 595 articles, 16 were included in the review. The most utilised machine learning models were random forest, support vector machines and XGBoost. The most commonly occurring variables were age, gender, measures of renal function, measures of proteinuria, and full blood examination. Only half of all studies included clinical variables in their models. The most important variables overall were measures of renal function, measures of proteinuria, age, full blood examination and serum albumin. Machine learning was consistently superior or non-inferior when compared to the Kidney Failure Risk Equation. This review identified key variables used in machine learning models to predict chronic kidney disease progression to kidney failure. These findings lay the foundations for the development of future machine learning models capable of rivalling the Kidney Failure Risk Equation in the provision of accurate kidney failure prediction.

1 | Introduction

Chronic Kidney Disease (CKD) is characterised by progressive injury and loss of kidney function over ≥3 months [1]. CKD affects more than 800 million people, confers a significant healthcare burden and is one of the leading causes of death worldwide [2, 3]. The final stage of CKD progression is known as Kidney Failure (KF), for which the mainstay of treatment is kidney replacement therapy (KRT) in the form of dialysis and transplantation [1].

Current trends in Australia indicate that the need for KRT is expected to increase significantly by 2030 [4]. This is on a background of a more than doubling in prevalence between 2000 and 2020 to over 27 000 people [5]. If such growth in demand for dialysis is realised, it would require an additional 800 dialysis chairs, potentially breaking an already strained system [4]. Such discordance between demand and capacity creates an environment where identifying those at greatest risk of progression to KF is of critical importance at both the individual and health service planning level.

Abbreviations: AI, artificial intelligence; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KF, kidney failure; KFRE, kidney failure risk equation; KRT, kidney replacement therapy; ML, machine learning; uACR, urinary albumin: creatinine ratio.

In those aged > 65 years old and with CKD, the risk of death is greater than the risk of progression to KF [6]. This raises the question of how to best stratify those who are likely to progress to KF and need KRT and those who are unlikely to progress to KF and would instead benefit from supportive care [6]. Given this imbalance, it is important to optimise the referral of CKD patients to nephrology services based on the likelihood of progression from CKD to KF. Early referral and consultation with a nephrologist is beneficial for those patients, delaying progression to KF [7]. However, the timing of referral is a difficult clinical decision given the heterogeneity of CKD progression.

Various methods have attempted to predict CKD progression to KF and aid the timing of referral. One such method is the Australian guidelines for referral of CKD patients to nephrology services [8]. These guidelines centre around an estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73 m^2 with consideration for urinary albumin: creatinine ratio (uACR), significant eGFR changes over time and the presence of resistant hypertension [8]. These guidelines are limited in their design and fail to integrate key prognostic parameters (demographic, clinical, biochemical) which may influence the trajectory of CKD progression. With this current pathway in place, 18% of patients who need KRT are referred late to nephrology services in Australia [9]. Methods such as the Kidney Failure Risk Equation (KFRE) by Tangri et al. [10] seek to integrate further data to enhance predictions of CKD progression, including age, sex, serum calcium, phosphate, albumin, and bicarbonate and has recently been validated in the Australian context [11]. However, the KFRE does not integrate change in eGFR over time and lacks integration of key predictive factors such as diabetes mellitus.

Artificial intelligence (AI), in particular machine learning (ML) models, have shown promise as a tool to optimise clinical decision making. CKD is a condition that generates large amounts of routinely collected clinical and biochemical data [12]. This makes it ideal for the integration of ML models designed to learn non-linear patterns in large, complex datasets and predict the outcome of future variables [13]. When building a ML model, the specific variables that are input into the model must be carefully considered as accuracy and data collection are heavily impacted by variable importance [14]. As a result, an understanding of the most important variables is vital to the development of any predictive ML model.

This narrative review employs a systematic search of the current literature to answer the question, what routinely collected data (demographic, clinical, and biochemical) can be integrated into ML models to optimise the referral of CKD patients so that those who are at greatest risk of KF are prioritised? The aim was to identify the most common and important variables used in ML models to predict progression of CKD to KF.

2 | Methods

2.1 | Electronic Searches

This study searched the following databases:

- Medline (via Ovid from January 2017 to August 2023)
- EMBASE (via Ovid from January 2017 to August 2023)

The search strategies are shown in Appendix A. A decision to limit the search from 2017 to 2023 was based on the novelty of the field. As shown in Figure 1, a review of the literature captured by our search strategy per year demonstrates a steady increase in the publications produced in this area across the last 5 years. The Boolean operator OR was used to combine search terms into population, ML model and outcome, the operator AND was used to combine these topics.

2.2 | Inclusion Criteria

- Adults aged ≥ 18 years.
- Population has CKD at baseline, defined as ≥ 3 months of kidney damage, eGFR ≤ 60 mL/min/1.73 m^2 or signs of kidney damage such as proteinuria, haematuria, blood or imaging abnormalities.
- ML is the focus of the predictive model.
- Measures KF as the outcome. Defined by eGFR, either ≤ 15 or ≤ 10 mL/min/1.73 m^2, commencement of KRT: dialysis or transplant.
- Describes variables incorporated into the model.

2.3 | Exclusion Criteria

- Non-English language paper.
- Study design is a review.
- Variables are not routinely collected or clinically translatable into a model. Includes imaging, insurance data, biopsy data, proteomics and metabolomics.

2.4 | Data Extraction

Data extraction was performed on studies that met the above criteria using a predetermined list, including title of paper and first author, year of publication, duration of data collection, region of study, demographics of included participants, sample sizes, type of ML model, most accurate model, comparison to non-ML predictors, variables used in the model, discussion of variable importance. Variables were then grouped into clinically relevant categories. For example, serum creatinine, eGFR, cystatin C, urea and blood urea nitrogen were grouped into 'measures of renal function'. Variables prior to grouping are shown in Table 3.

3 | Results

The systematic search is summarised in Figure 2. The search, which was conducted in August 2023, yielded 595 articles (432 EMBASE, 163 Medline). After removal of duplicates 522 articles underwent title and abstract screening for eligibility. Following

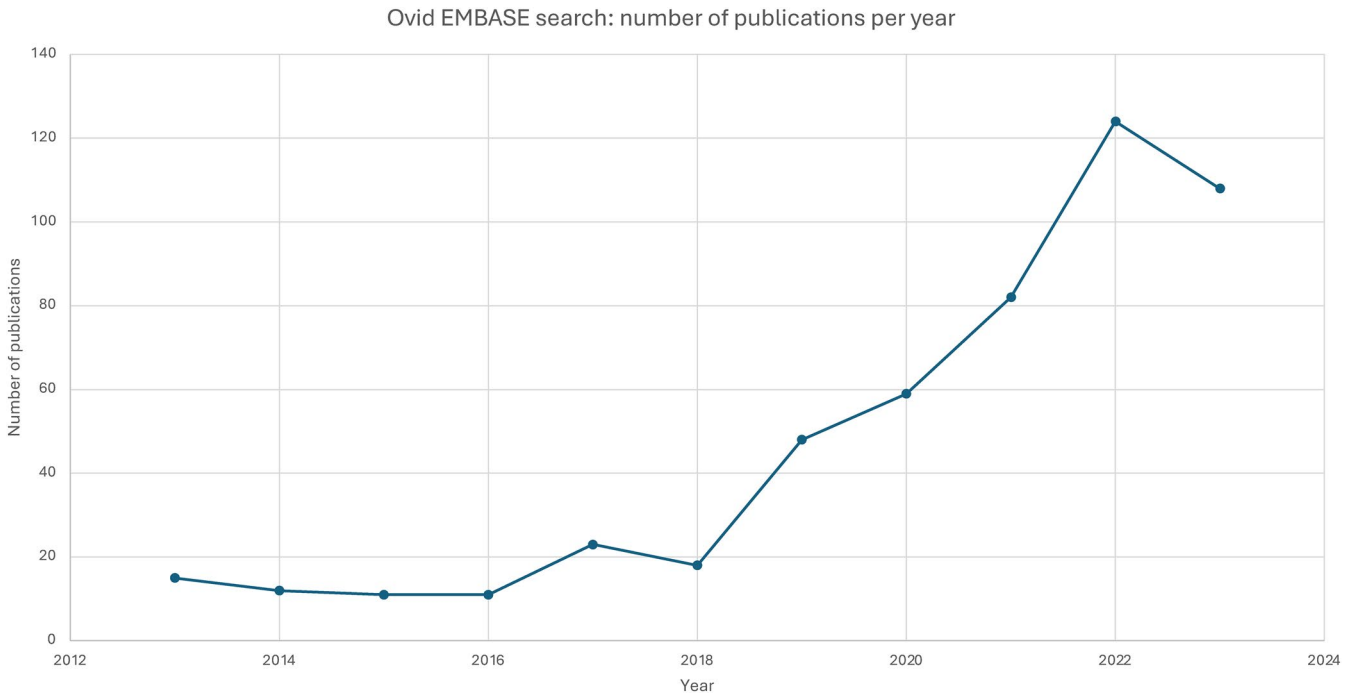

FIGURE 1 | Number of publications per year via Ovid Embase that meet the search terms. Number of publications is lowest in 2015 and 2016 with 11 publications meeting search terms and highest in 2022 with 124 publications meeting search terms. As of August, 104 publications meet search criteria in 2023.

this, 46 articles were submitted to full text screening. The full text articles were reviewed, after which 16 met the inclusion criteria and were included in this review. The included studies are summarised in Tables 1–3.

3.1 | Study Characteristics

The included studies represent modelling on 297 185 patients with CKD. The largest sample size was 184 293 [15] and the smallest was 436 [16] with an average of 18 574 patients. The average age and baseline eGFR were highly variable across studies. The eGFR ranged from 24.3 mL/min/1.73 m^2 in the Su et al. [17] late-stage cohort to 86 mL/min/1.73 m^2 in the Ferguson et al. [15] validation cohort. Average age ranged from 44.89 [18] to 81.35 [19] years.

3.2 | Machine Learning Models

The most commonly used types of ML models were random forest (RF), support vector machines (SVM) and XGBoost used in 9 [15, 17, 18, 20–25], 7 [16–18, 21, 24–26] and, 6 [17, 18, 22, 24, 26, 27] studies, respectively. RF was also the ML model that ranked consistently as the most accurate. When studies reported utilising multiple ML models, RF was the most accurate on 4 occasions with an area under the curve (AUC) ranging from 0.81 to 0.97 [17, 20, 22, 25], where the closer the AUC to 1.0 the more accurate the model.

Four of 6 studies demonstrated superior predictive capacity when compared to KFRE [21, 26–28]. KFRE demonstrated equivalent predictive capacity in 1 study [20], and equivalent 24-month KF prediction in another [29]. However, ML was superior in this study when predicting 6-month progression.

3.3 | Variable Occurrence

3.3.1 | Demographic Variables

The most common demographic variables, illustrated in Figure 3A, were age [15–30] and sex [15–27, 29, 30] occurring in 16 and 15 studies, respectively. Comorbidities and smoking status were commonly reported. Hypertension (HTN) occurred in 11 studies [16–20, 22–26, 29]; diabetes mellitus (DM) was a variable in 9 studies [16–20, 22, 24, 26, 29]. Vascular disease, including cardiovascular disease, peripheral vascular disease, coronary artery disease and cerebrovascular disease occurred in 7 papers [16, 17, 19, 20, 22, 25, 29]. Smoking status was reported in 5 studies [16, 20, 21, 24, 29] and CKD aetiology were considered in 4 studies [20, 25, 29, 30].

The use of specific medications was used as a variable in 3 studies [16, 22, 24]. Dyslipidaemia [16, 18], comorbidity analysis [24, 30], history of anaemia [16, 23], number of hospitalisations [24, 29], and socioeconomic status (SES) were variables in 2 studies [16, 20].

There were numerous infrequently occurring demographic variables, only reported in single studies. This included date of death [27], use of alcohol [20], cardiopathy [23], chronic obstructive pulmonary disease, congestive cardiac failure, connective tissue disorder, dementia, liver disease, gout [29], exercise habit [16], and history of urolithiasis [18].

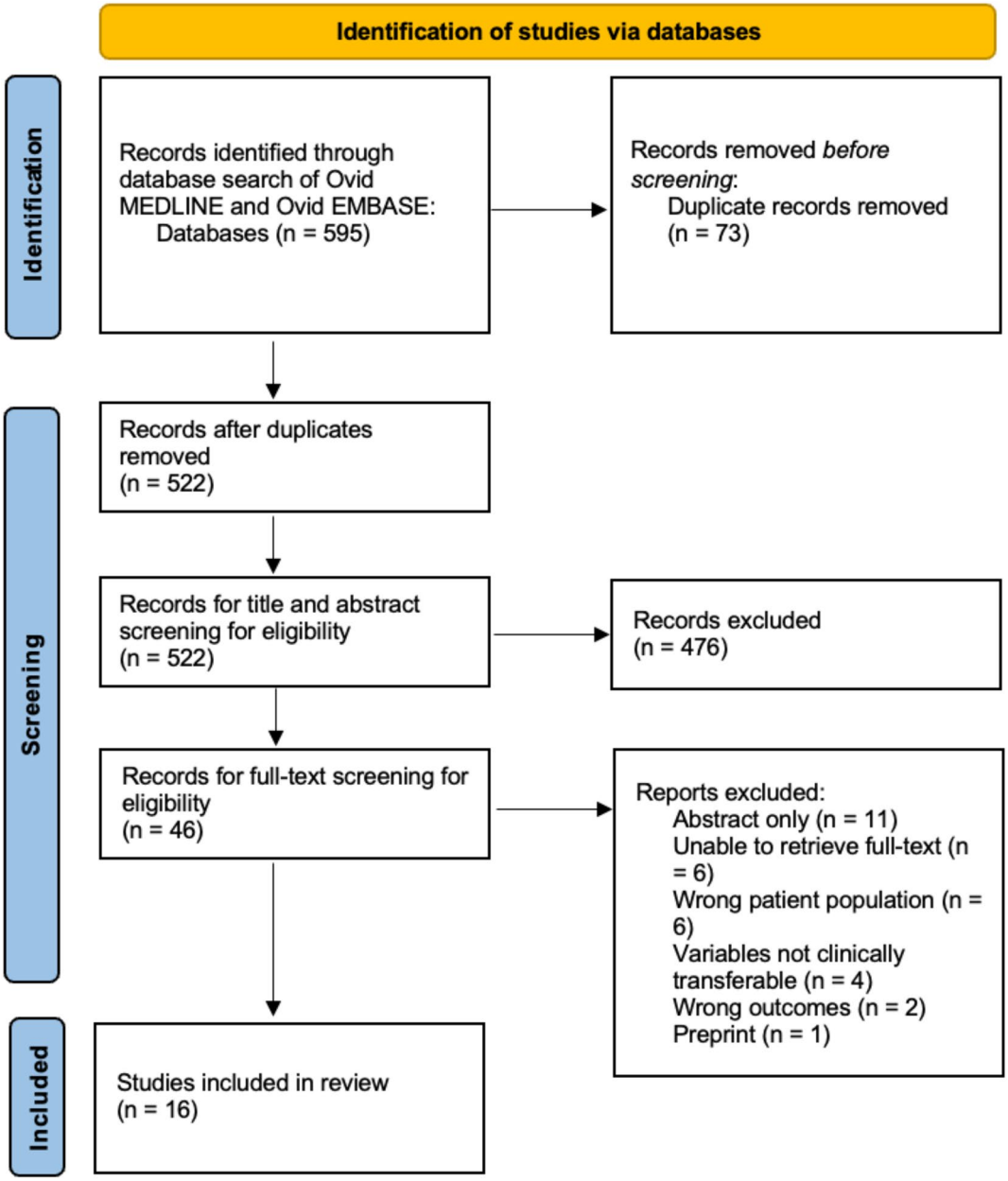

FIGURE 2 | PRISMA flow diagram.

3.3.2 | Clinical Variables

The occurrence of clinical variables is depicted in Figure 3B. In total, 8 out of 16 studies integrated clinical variables into their models [16, 17, 19–21, 24, 27, 29]. The most commonly occurring clinical variable was blood pressure, and body mass index/height/weight, both occurring in the 8 previously listed studies. Heart rate [27], and waist/hip circumference were mentioned in 1 study [16].

3.3.3 | Biochemical Variables

The most frequently occurring biochemical variables are shown in Figure 3C. Measures of renal function occurred most frequently, appearing in 15 of the 16 studies [15–29]. The second most commonly occurring set of variables was full blood examination (FBE) reported in 14 studies [15–18, 20–26, 28–30] followed by measures of proteinuria which occurred in 13 studies [15–19, 21, 22, 24–29]. Chemistry panels, comprising sodium and potassium, were integrated in 11 studies [15, 16, 18, 20–23, 25, 26, 29, 30]. Diabetic markers [16–21, 24, 25, 27, 28] and lipids [16–18, 20–22, 24, 25, 28, 30] were seen in 10 studies, whilst serum albumin was reported in 9 studies [16, 18, 20–22, 24, 26, 28, 29].

Half of the 16 studies integrated measures of liver function [15, 16, 18, 20, 23–25, 30], CMP/PTH (Calcium, magnesium and phosphate/ parathyroid hormone) [16–18, 20–22, 29, 30] and uric acid as variables in their ML models [16, 18, 20–23, 25, 30].

Less common variables included a urine screen including vitamins and specific gravity in 4 studies [17, 23, 25, 28]. Iron studies [16, 29], C-reactive protein (CRP) [24, 28] and bicarbonate

TABLE 1 | Baseline demographics of included studies.

Author/year	Region	Sample size	Data collection period	Demographics
Bai, Q. et al. 2022 [20]	China	748	Apr 2006–Dec 2015	**Age**: 57.8 years **Sex**: 56% male **eGFR**: 46.1 mL/min/1.73^2 **Comorbidity**: HTN 74.6%; DM 55.5%, vascular disease 23.7%
Bellocchio, F. 2021 [29]	Multinational	**FMC NephroCare**: 24535 (70% Development, 30% Validation) **GCKD**: 4058	**FMC NephroCare**: 2017–2018 **GCKD**: Jul 2011–2012	**FMC NephroCare cohort** **Age**: 72.15 years **Sex**: 50.36% male **eGFR**: 31.93 mL/min/1.73^2 **Comorbidity**: HTN 79.3%; DM 40.03%, CAD 19.24% **GCKD cohort** **Age**: 62.12 years **Sex**: 61.85% male **eGFR**: 41.92 mL/min/1.73^2 **Comorbidity**: HTN 97.38%; DM 38.07%, CAD 22.38%
Cheng, L. 2017 [16]	Taiwan	436	Jan 2004–Dec 2013	**Age**: 71.91% ≥ 65 years **Sex**: ≥ 65 years group 48.65% male **Comorbidity**: NR
Chuah, A. 2022 [27]	Australia	2388 (80% train, 20% test)	Sept 1996–Mar 2018	**Train cohort** **Age**: 62 years **Sex**: 58% male **eGFR**: NR. (30% stage 2 CKD) **Comorbidity**: NR **Test cohort** **Age**: 64 years **Sex**: 57% male **eGFR**: NR. (32% stage 2 CKD) **Comorbidity**: NR

(Continues)

TABLE 1 | (Continued)

Author/year	Region	Sample size	Data collection period	Demographics
Ferguson, T. 2022 [15]	Canada	**Development cohort:** 77196. (70% training, 30% testing) **Validation cohort:** 107097	**Development:** Apr 2006–Dec 2016 **Validation:** Apr 2009–Dec 2016	**Development** **Age**: 59.3 years **Sex**: 48% male **eGFR**: 82.2 mL/min/1.73^2 **Comorbidity**: HTN 70%; DM 45%, MI 3% **Validation** **Age**: 55.5y **Sex**: 53% male **eGFR**: 86 mL/min/1.73^2 **Comorbidity**: HTN 51%; DM 41%, MI 6%
Hui, M. 2023 [26]	China	**Development:** 3216 (Training 70%, testing 30%) **Validation:** 342	**Development**: Nov 2011–Dec 2017 **Validation**: Jan 2003–Dec 2020.	**Development** **Age**: 48 years **Sex**: 59.4% male **eGFR**: 52.97 mL/min/1.73^2 **Comorbidity**: HTN 73.5%; DM 19.9%, CVD 8.4% **Validation** **Age**: 55 years **Sex**: 38.9% male **eGFR**: 50.83 mL/min/1.73^2 **Comorbidity**: HTN 24.3%; DM 28.9%, CVD 2%
Kanda, E. 2021 [22]	Japan	**Development:** 3714 Baseline 80%—2967 Selection data set—747 **Validation:** 26906	**Development**: Jan 2014–Dec 2017 **Validation**: Jan 2018–Dec 2020	**Development** **Age**: 60.1 years **Sex**: 53.1% male **eGFR**: 54.2 mL/min/1.73^2 **Comorbidity**: HTN 50.6%; DM 23.1%, CVD 9.8% **Validation** **Age**: 61.2 years **Sex**: 51.2% male **eGFR**: 73.1 mL/min/1.73^2 **Comorbidity**: HTN 20.7%; DM 21%, CVD 0.7%
Liang, P. 2023 [18]	China	1765	Jan 2009–Dec 2020	**Age**: 44.89 years **Sex**: 59% male **eGFR**: 66.3 mL/min/1.73^2 **Comorbidity**: HTN 36%; DM 34%

(Continues)

TABLE 1 | (Continued)

Author/year	Region	Sample size	Data collection period	Demographics
Liao, C. M. 2023 [19]	Taiwan	497	Nov 2006–Dec 2019	**Age**: 81.35 years **Sex**: 65% male **eGFR**: 36.72 mL/min/1.73^2 **Comorbidity**: HTN 70%; DM 53%, CVD 14%
Nagarj, B. 2020 [21]	Multinational	**RENAAL**: 1513 **IDNT**: 1715 **ALTITUDE**: 8561	**RENAAL**: 1996–1998 **IDNT**: 1996–1998 **ALTITUDE**: Oct 2007–Feb 2013	**RENAAL** **Age**: 60 years **Sex**: approx. 63.2% male **eGFR**: NR ml/min/1.73^2 **Comorbidity**: HTN 96.5%; DM NR%, MI approx. 11.1% **IDNT** **Age**: 58.9 years **Sex**: 66.8% male **eGFR**: 66.1 mL/min/1.73^2 **Comorbidity**: HTN 100%; DM 100%, CAD 16.5% **ALTITUDE** **Age**: approx. 64.5 years **Sex**: approx. 68% male **eGFR**: 57 mL/min/1.73^2 **Comorbidity**: HTN 94.5%; DM 100%, CVD approx. 21.2%
Su, C. T. 2022 [17]	Taiwan	858	Nov 2006–Dec 2019	**Early-stage CKD** **Age**: 80.8 years **Sex**: 70% male **eGFR**: 55.3 mL/min/1.73^2 **Comorbidity**: HTN 23%; DM 53%, CVD 59% **Late-stage CKD** **Age**: 79.4 years **Sex**: 66.4% male **eGFR**: 24.3 mL/min/1.73^2 **Comorbidity**: HTN 76%; DM 53.5%, CVD 7%
Vertrella, P. 2021 [23]	Italy	906	Since early 2000's	**Age**: 68 years **Sex**: 68% male **eGFR**: NR ml/min/1.73^2 **Comorbidity**: HTN 74%; DM 41%

(Continues)

TABLE 1 | (Continued)

Author/year	Region	Sample size	Data collection period	Demographics
Wang, S. 2022 [24]	Korea	19 159	EMR data since 2003	**Age**: 62.3 years **Sex**: 55.7% male **eGFR**: 76.7 mL/min/1.73^2 **Comorbidity**: HTN 87.2%; DM 100%
Yuan, Q. J. 2020 [25]	China	1090	Aug 2010–Apr 2018	**Age**: 50.01 years **Sex**: 56.3% male **eGFR**: 45.6 mL/min/1.73^2 **Comorbidity**: HTN 30.6%; DM NR%, CVD 2.7%
Zacharias, H. U. 2022 [28]	Europe	**Development**: GCKD 4915 (Training: 3276, testing: 1639) **Validation**: CDK-REIN, 1912; SKS 949; MMKD 202	**GCKD** Mar 2010–Mar 2012 **CKD-REIN** Jul 2013–Jul 2021 **SKS** 2002–Mar 2018 **MMKD** NR	**GCKD** **Age**: 60 years **Sex**: 60.2% male **eGFR**: 49.9 mL/min/1.73^2 **Comorbidity**: HTN 96.1%; DM 26.4%, vascular disease 22.4% **CDK-REIN** **Age**: 66.21 years **Sex**: 66.7% male **eGFR**: 34.13 mL/min/1.73^2 **Comorbidity**: HTN 90.8%; DM 42.3%, vascular disease 39.3% **SKS** **Age**: 65.20 years **Sex**: 62.8% male **eGFR**: 30.81 mL/min/1.73^2 **Comorbidity**: HTN 93.9%; DM 29.3%, vascular disease 32.3% **MMKD** **Age**: 46.33 years **Sex**: 65.8% male **eGFR**: 47.4 mL/min/1.73^2 **Comorbidity**: HTN 89.1%; DM 0%, vascular disease 11.9%

(Continues)

TABLE 1 | (Continued)

Author/year	Region	Sample size	Data collection period	Demographics
Zhou, F. 2020 [30]	United States	2507	Jan 2003–Dec 2011	**High risk group** **Age**: 67 years **Sex**: 52% male **eGFR**: NR (CKD stage 3) ml/min/1.73^2 **Comorbidity**: HTN NR%; DM 47.1%, CAD 25% **Low risk group** **Age**: 75 years **Sex**: 44.3% male **eGFR**: NR (CKD stage 3) ml/min/1.73^2 **Comorbidity**: HTN NR%; DM 26.4% (with renal manifestation), CAD 33%

Abbreviations: ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints; CAD, coronary artery disease; CKD, chronic kidney disease; CKD-REIN, Chronic Kidney Disease Epidemiology and Information Network; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EMR, electronic medical record; GCKD, German Chronic Kidney Disease; HTN, hypertension; IDNT, Irbesartan Diabetic Nephropathy Trial; MI, myocardial infarction; MMKD, Mild to Moderate Kidney Disease; NR, not recorded; RENAAL, Reduction of Endpoints in NIDDM (Non-insulin dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan; SKS, Salford Kidney Study.

[20, 30] occurred twice as a variable, whilst vitamin D was reported in 1 study [30].

3.4 | Variable Importance

In total, 11 of the 16 studies assessed variable importance (Figure 4) [15–19, 21–25, 27]. A ratio of the number of times a variable was reported within the top five variables of a study, and the number of studies that assessed variable importance was used to analyse the overall significance of a variable.

The most important variable seen across this search was measures of renal function with a ratio of 0.91, occurring within the top five most important variables in 10 out of 11 studies. The next most important variables identified were measures of proteinuria, age, FBE values and albumin with ratio values of 0.64, 0.55, 0.45 and 0.45, respectively. Other variables, ranked within the top five most important variables in 3 of 11 studies were BP, chemistry panel, diabetic markers, lipids, CMP and sex.

4 | Discussion

ML is a promising tool to predict the progression of CKD to KF. This analysis of the literature has identified the common and important variables used in ML models to predict progressive CKD.

4.1 | Variables Used in Predictive ML Models

The identified variables primarily relate to three broad categories. First, variables related to overall kidney function such as measures of renal function and proteinuria. Second, variables related to complications of CKD, such as the FBE, chemistry panel and CMP/PTH. Finally, factors associated with potential CKD aetiologies such as diabetic markers, lipid levels, and history of HTN, DM and vascular disease.

It is not surprising that the most commonly occurring variables in these models directly relate to renal function. Measures of renal function (including eGFR and serum creatinine), as well as measures of proteinuria, were the most commonly occurring variables as well as the most important in these ML models. Indeed, proteinuria has long since been identified as an independent risk factor for the progression of CKD [31].

Variables related to the consequences of CKD featured heavily across the identified studies. Again, this was not a surprise, the information contained within an FBE provides vital information directly related to anaemia of CKD seen in the latter stages of CKD [32]. Metabolic bone disease and electrolyte derangement are additional common complications of CKD and support the inclusion of these variables into observed models [33].

Serum albumin was identified by this study as one of the top five most important variables across the included literature. This is a variable which does not fit in the previously described broad categories. There have been various hypotheses as to why serum albumin is influential in these models. Haller's paper published

TABLE 2 | Machine learning models used in included studies.

Author/ year	Type of ML model(s) used	Most accurate model (accuracy)	Non-ML comparison
Bai, Q. et al. 2022 [20]	LR RF Naïve Bayes DT K-nearest neighbours	RF (AUC 0.81)	KFRE = ML model (AUC 0.80)
Bellocchio, F. 2021 [29]	Naïve Bayes classifier	**FMC NephroCare validation**: 6-month (AUC 0.90), 24-month (AUC 0.85) **GCKD**: 6-month (AUC 0.91), 24-month (AUC 0.85)	KFRE < ML for 6-month prediction KFRE = ML for 24-month prediction Clinical prediction < ML for 24-month prediction
Cheng, L. 2017 [16]	C4.5 CART SVM	CART (AUC ranged 0.6–0.7)	Creatinine model < ML
Chuah, A. 2022 [27]	XGBoost	86.2% prediction accuracy	KFRE < ML Clinician prediction < ML
Ferguson, T. 2022 [15]	RF	1-year AUC 0.90, 5-year AUC 0.84	NR
Hui, M. 2023 [26]	XGBoost SSVM	XGBoost 2 year (AUC 0.83), 5 year (AUC 0.91)	Cox < ML KFRE < ML
Kanda, E. 2021 [22]	RF Gradient boosting descision tree XGBoost	RF (AUC approx. 0.9)	NR
Liang, P. 2023 [18]	DNN LR RRC LASSO SVM-Radial Basis Function SVM-linear RF XGBoost	DNN (AUC 0.90)	NR
Liao, C. M. 2023 [19]	Cox PHM RSF ANN	RSF (average C-index 0.89)	NR
Nagarj, B. 2020 [21]	LR SVM with Gaussian kernel RF FNN	FNN: AUC 0.82 (RENAAL), 0.81 (IDNT), 0.84 (ALTITUDE)	Cox proportional hazards regression < ML KFRE < ML
Su, C. T. 2022 [17]	Logistic regression Random forest XGBoost SVM GNB classifier	RF, early-stage (AUC 0.96), late-stage (AUC 0.97)	NR
Vertrella, P. 2021 [23]	LR DT RF, Extremely randomised trees, gradient tree boosting NN	Extremely randomised trees (Accuracy 94%)	NR

(Continues)

TABLE 2 | (Continued)

Author/ year	Type of ML model(s) used	Most accurate model (accuracy)	Non-ML comparison
Wang, S. 2022 [24]	XGBoost SVM DT RF	XGBoost, (AUROC curve 0.95)	NR
Yuan, Q. J. 2020 [25]	RF SVM LR NN	RF, 3a progression (AUC 0.88), 3b progression (AUC 0.83)	NR
Zacharias, H. U. 2022 [28]	LASSO cox proportional hazards models	2-year C-statistic 0.91 in development cohort. C-statistic ranged from 0.89–0.92 in validation cohorts	KFRE < ML
Zhou, F. 2020 [30]	NLP	NLP, (71% accuracy)	NR

Abbreviations: *AUC*, area under the curve; *CART*, classification and regression tree; *DT*, decision tree; *GCKD*, German Chronic Kidney Disease; *GNB*, Gaussian naïve Bayes; *KFRE*, Kidney Failure Risk Equation; *LASSO*, least absolute shrinkage and selection operator; *LR*, logistic regression; *ML*, machine learning; NLP, natural language processing; *NN*, neural network; *NR*, not recorded; *RF*, random forest; *SSVM*, smooth support vector machine; *SVM*, support vector machine.

in 2006, [34] described a state of systemic inflammation in the latter stages of CKD which caused a reduction in the production of albumin and an increase in degradation of this protein. Further studies have supported this association between hypoalbuminemia and progressive CKD whilst suggesting that albumin may further the inflammatory state by driving cytokine production [35, 36]. There is also consideration for the albumin as a marker of an individual's nutritional state, as CKD progresses and individuals become more malnourished albumin may decline [37]. Measures of liver function were an additional variable with greater occurrence than expected. These variables were included in the models of half of the included studies and were reported within the top five most important features in 2 studies. Low serum bilirubin has previously been reported as a risk factor for the development of CKD in a Japanese population [38]. The authors theorised that this may be related to the antioxidant nature of bilirubin and the downstream role this has on atherosclerotic disease.

Variables related to CKD aetiology featured heavily within the included models. This was in the form of binary variables such as a history of diabetes or continuous variables such as HbA1c values. As diabetes and hypertension are the leading causes of CKD their inclusion in these models is logical [39]. However, is it surprising that despite correlating with the progression of CKD [40], blood pressure measurements were only utilised in half of the included studies. It may be that the researchers felt blood pressure recorded in the clinic to not be an accurate representation of an individual's true blood pressure. This may explain why a variable perceived as a more accurate test such as HbA1c was integrated into ML models at a greater frequency than blood pressure despite similar variable importance found within this review and the literature [41].

Age and sex were additional variables that featured highly in terms of frequency and importance. As discussed earlier, age demonstrates a strong negative association with the chance of progression to KF due to competing risk of death [6]. When developing predictive algorithms, the impact of competing risks strongly influences accuracy. This review explored CKD progression to KF, for which death is a major competing risk. Whilst age is considered in many of the included studies, there is little consideration for other variables that influence competing risk of death such as commencement of renal protective medication or assessment of geographic access to healthcare similar to the recent Aus CVD Risk calculator [42]. Consideration for competing risks gains greater significance when factoring in the impact of censoring or including said risk. The consequence being the accuracy of predicting an endpoint being determined on incomplete data [43]. Sex is important to consider as progression to KF appears to be slower in women when compared to men [44]. The exact mechanism for these differences is uncertain, although several hypotheses have been proposed in relation to sex hormones and nitric oxide metabolism [44].

It should be noted that there were highly variable reporting techniques across the included studies. Common comorbidities such as hypertension and diabetes mellitus were routinely reported in baseline cohort data. However, beyond this, there was little consistency. Common associated comorbidities, such as dyslipidaemia, were not routinely reported in baseline data. Moreover, the description of features included in the ML models was highly variable. For example, a general 'chemistry panel' was listed in some studies, whereas others specified 'sodium and potassium' only. Similarly, 'HbA1c' and 'sugar [AC]' were used interchangeably between studies.

4.2 | Comparison to KFRE

The KFRE is a clinical tool that predicts 2- and 5-year risk of KF [10]. This tool has been widely validated and is the most widely used model clinical model to predict CKD progression to KF. This makes it a key comparison for any ML model looking to predict progression to KF. The data supports ML models as having a greater predictive value than the KFRE in predicting progressive CKD.

TABLE 3 | Machine learning variables used in included studies.

Author/year	Demographic	Biochemical	Clinical	Discusses variable importance
Bai, Q. et al. 2022 [20]	Age, sex, educational level, marriage status, insurance status, CKD aetiology, History of DM, HTN, CVD. Smoking and alcohol status	Serum creatinine, UA, BUN, WCC, Hb, platelets count, ALT, AST, TP, albumin, ALP, HDL, LDL, TG, TC, Ca^{2+}, phosphorus, K^+, Na^+, Cl^-, and $HCO_{3\_}$, eGFR	BMI, SBP, DBP	No
Bellocchio, F. 2021 [29]	Age, sex, smoking status, CKD aetiology, History of cerebrovascular disease, COPD, CCF, connective tissue disorder, CAD, dementia, DM, hemiplegia, HTN, liver disease, PVD, number of hospitalisations	Serum albumin, uACR, Ca^{2+}, eGFR, regressGFR, Hb, Phosphate, urine protein, PTH, Na^+, ferritin	BMI, SBP	No
Cheng, L. 2017 [16]	Age, sex, use of Chinese herbs, analgesics, health education, behavioural appraisal, cognitive appraisal, habits such as smoking, alcohol, exercise, betel quid chewing. History of DM, HTN, CVD, high cholesterol, gout, anaemia	Creatinine, BUN, Hb, Hct, WBC, RBC, Ca^{2+}, Phosphate, Na^+, K^+, Cl^-, Mg^{2+}, UA, Cholesterol, TG, serum albumin, PTH, TP, HbA1c, Urine Protein, HDL-Cholesterol, LDL-Cholesterol, Fe, Ferritin, uACR, Ca×P	Height, Weight, Waist circumference, Hip circumference, SBP, DBP	Yes
Chuah, A. 2022 [27]	Age, sex, date of death	Creatine, eGFR, glucose, HbA1c, uPCR, 24 h proteinuria	Sitting and standing BP, HR, weight, height, BMI, sitting and standing pulse pressure	Yes
Ferguson, T. 2022 [15]	Age, Sex	eGFR, uACR, Chemistry panel, liver enzymes, complete blood panel	NR	Yes
Hui, M. 2023 [26]	Age, Sex, History of DM, HTN	eGFR, uACR, serum albumin, Hb	NR	No
Kanda, E. 2021 [22]	Age, sex, History of DM, HTN, CVD, Use of renin-angiotensin-aldosterone system inhibitors, phosphorus absorbents, vitamin D, statins, UA-lowering medicines, and EPO-stimulating agents.	eGFR; serum albumin, Na^+, K^+, calcium, phosphorus, LDL, and UA levels; WCC; Hb; uPCR	NR	Yes
Liang, P. 2023 [18]	Age, sex, History of DM, HTN, urolithiasis, hyperlipidaemia	eGFR, serum creatinine, BUN, UA, WBC count, RBC count, Hb, serum albumin, AST, ALT, Na^+, K^+, Ca^{2+}, phosphorus, Cl^-, cholesterol, TG, glucose, uACR	NR	Yes
Liao, C. M. 2023 [19]	Age, sex, History of HTN, DM, CVD	Serum creatinine, eGFR, uPCR, HbA1c	BMI, SBP, DBP	Yes

(Continues)

TABLE 3 | (Continued)

Author/year	Demographic	Biochemical	Clinical	Discusses variable importance
Nagarj, B. 2020 [21]	Age, sex, Smoking status, History of CVD	Serum creatinine, K+, Hb, HbA1c, serum albumin, Cl^-, phosphorous, UA, HDL, LDL, uACR	BMI, SBP, DBP	Yes
Su, C. T. 2022 [17]	Age, Sex, History of DM, HTN, CVD	eGFR, Hb, Hct, serum creatinine, BUN, Na+, K^+, Ca^{2+}, phosphorus, uPCR, lipid profile, HbA1c	Blood pressure, Height, Weight	Yes
Vertrella, P. 2021 [23]	Age, sex, History of anaemia, cardiopathy, HTN	AST, Cl^-, serum creatinine, creatinine delta, erythrocytes, erythrocytes delta, GFR delta last 4 months, GFR delta last year, GFR standard deviation last 4 months, GFR standard deviation last year, Hct, Hb, last GFR, MCV, MCH, K^+, Na^+, specific gravity standard deviation, urate, urea, urea delta	NR	Yes
Wang, S. 2022 [24]	Age, sex, HTN, DM, smoking, visit history, insulin, metformin, anti-HTN, lipid lowering, anti-platelet, anti-coagulant, Charlson comorbidity index	TC, HDL-cholesterol, LDL-cholesterol, TG, serum creatinine, serum albumin, uACR, AST, ALT, insulin, HbA1c, fbs, pp2, apo_a1, apo_b, lipoprotein, CRP, c-peptide, and platelets, LFTs	Height, weight, SBP, DBP	Yes
Yuan, Q. J. 2020 [25]	Age, sex, History of HTN, CVD, CKD aetiology	Urine screen: bilirubin, WBC, vitamin C, specific gravity, nitrite, glucose, ketone bodies, pH, urobilinogen FBE, LDL, HDL/TC, TG, Serum urea, UA, Bile acids, LFTs, UEC, bile acid, Cl^-, glucose, eGFR	NR	Yes
Zacharias, H. U. 2022 [28]	Age	Serum creatinine, serum cystatin C, uACR, serum urea, Hb, serum albumin, CRP, Na^+, HbA1c, HDL, LDL, urine creatinine, eGFR	NR	No
Zhou, F. 2020 [30]	Age, sex, comorbidity clusters, CKD aetiology	Vitamin D, $HCO_{3\_}$, Ca^{2+}, Hct, K^+, Na^+, TP, PTH, TG, uPCR, UA	NR	No

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BUN, blood urea nitrogen; Ca^{2+}, calcium; CAD, coronary artery disease; CCF, congestive cardiac failure; CKD, chronic kidney disease; Cl^-, chloride; CMP, calcium magnesium phosphate; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HbA1c, glycated haemoglobin; $HCO_{3\_}$, bicarbonate; Hct, haematocrit; HDL, high-density lipoprotein; HTN, hypertension; K^+, potassium; LDL, low-density lipoprotein; Mg^{2+}, magnesium; Na^+, sodium; NR, not recorded; PTH, parathyroid hormone; PVD, peripheral vascular disease; RBC, red blood cell; RCC, red cell count; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TP, total protein; UA, uric acid; uACR, urinary albumin: creatinine ratio; uPCR, urinary protein: creatinine ratio; WBC, white blood cell; WCC, white cell count.

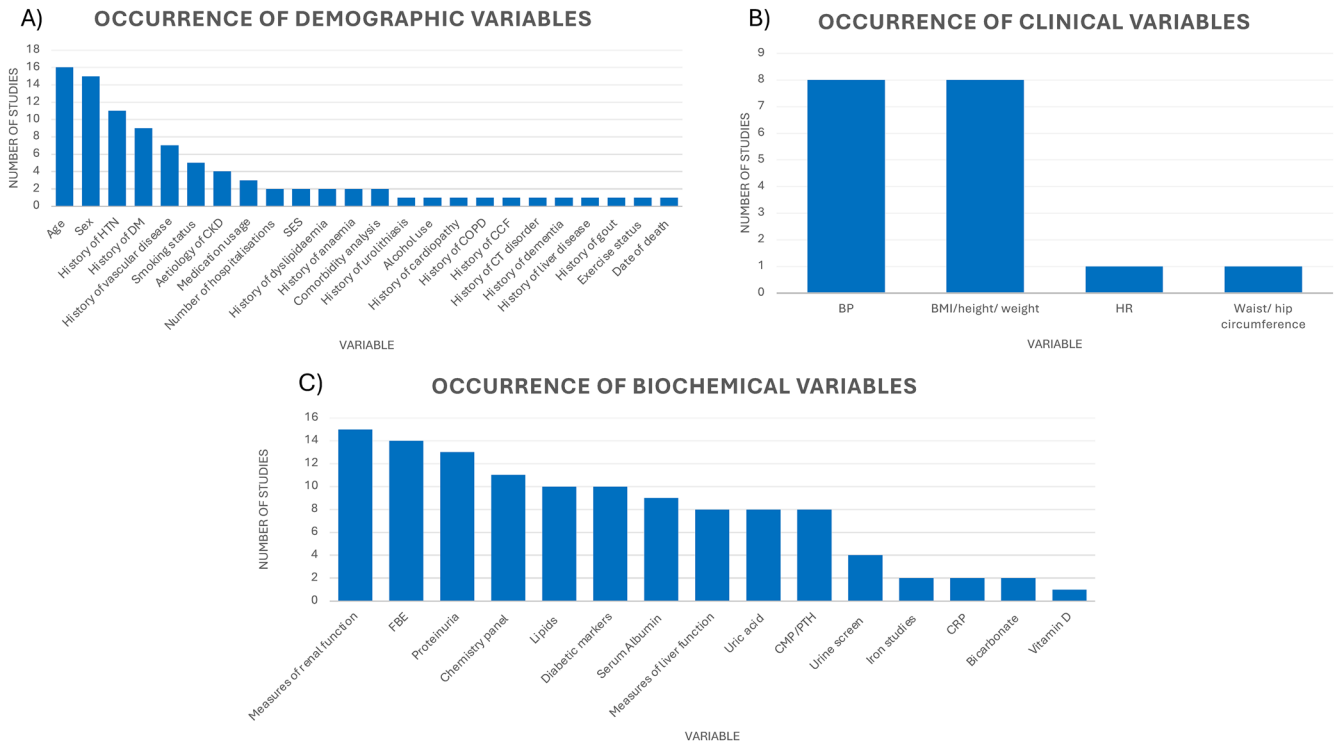

FIGURE 3 | Variable occurrence. (A) Vascular disease included cardiovascular disease, peripheral vascular disease, coronary artery disease, cerebrovascular disease. Aetiology of CKD included hypertension, diabetes, glomerulonephritis, polycystic kidney disease. Medication usage included use of statin, Chinese herbs, analgesic, renin-angiotensin-aldosterone system inhibitor, phosphorous binder, vitamin D supplementation, uric acid lowering medication, erythropoietin stimulator, insulin, metformin, anti-hypertensive, anti-platelet, anti-coagulant. SES includes marriage and insurance status, health, behavioural and cognitive appraisal. *HTN*; hypertension, *DM*; diabetes mellitus, *CKD*; chronic kidney disease, *SES*; socioeconomic status, *COPD*; chronic obstructive pulmonary disease, *CCF*; congestive cardiac failure, *CT*; connective tissue. (B) Blood pressure includes systolic and diastolic blood pressures. *BP*; blood pressure, *BMI*; body mass index, *HR*; heart rate. (C) Measures of renal function included eGFR, serum creatinine, serum urea/ blood urea nitrogen and cystatin C. Full blood examination including red blood cell count, white blood cell count, haemoglobin, haematocrit, red blood cell distribution width, platelet count, monocyte % mean corpuscular volume and mean corpuscular haemoglobin. Proteinuria included urine albumin creatinine ratio, urine protein creatinine ratio, urinary total protein and 24-h urine protein. Chemistry panels including sodium and potassium. Lipids included total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein and apo, diabetic markers included haemoglobin A1C, glucose, c-peptide and insulin level. Measures of liver function included liver function tests, alanine aminotransferase, aspartate aminotransferase, total protein. Urine screen included Vitamin C, bilirubin, white blood cell, specific gravity, ketone bodies, glucose, pH, nitrite, urobilinogen and Cr. Iron studies included Ferritin and iron. *FBE*; full blood examination, *CMP/PTH*; Calcium, magnesium and phosphate/ parathyroid hormone, *CRP*; C-reactive protein.

ML models allow the integration of key predictive factors that are not represented in the KFRE, such as a history of hypertension, diabetes, and vascular disease, as well as biochemical data relating to these comorbidities such as HbA1c. This study found that ML was consistently, albeit in only 6 studies to date, non-inferior [20, 29] or superior [21, 26–28] when compared to KFRE. Of note, the KFRE model integrates bicarbonate into its algorithm, which was only evident in 2 ML studies and ranked as important in one. This is interesting given acidosis arising as serum bicarbonate falls is correlated with a declining eGFR [45] and may be a consequence of the study cohorts captured by this review. Moreover, bicarbonate declines with age in individuals aged over 60 years. As this is a similar age group to those who are at greater risk of mortality than progression to KF [6], the predictive value may be limited.

One of the limitations of the KFRE is that it only integrates variables that represent a single point in time. This review has demonstrated that ML offers the potential for the integration of variables with a time component. This was done in several different ways including temporal abstraction techniques [16], eGFR slope [23, 29] and eGFR standard deviation over 4 and 12 months [23]. When integrated into these models, time-dependent variables exerted major effects on model performance [16, 19]. An additional limitation of the KFRE is the failure to consider competing risks. This had led to the development of models such as KD Predict with superior predictive capacity when compared to the KFRE [46]. In a similar manner, the consideration of age within ML predative models may further explain the comparatively superior KF predictive accuracy. Resultingly, the integration of time into ML models should be explored when developing future models.

4.3 | Strengths and Limitations

To the author's knowledge, this review is the first to elucidate the most important variables (demographic, clinical, biochemical) used in ML models to predict the progression of CKD to KF.

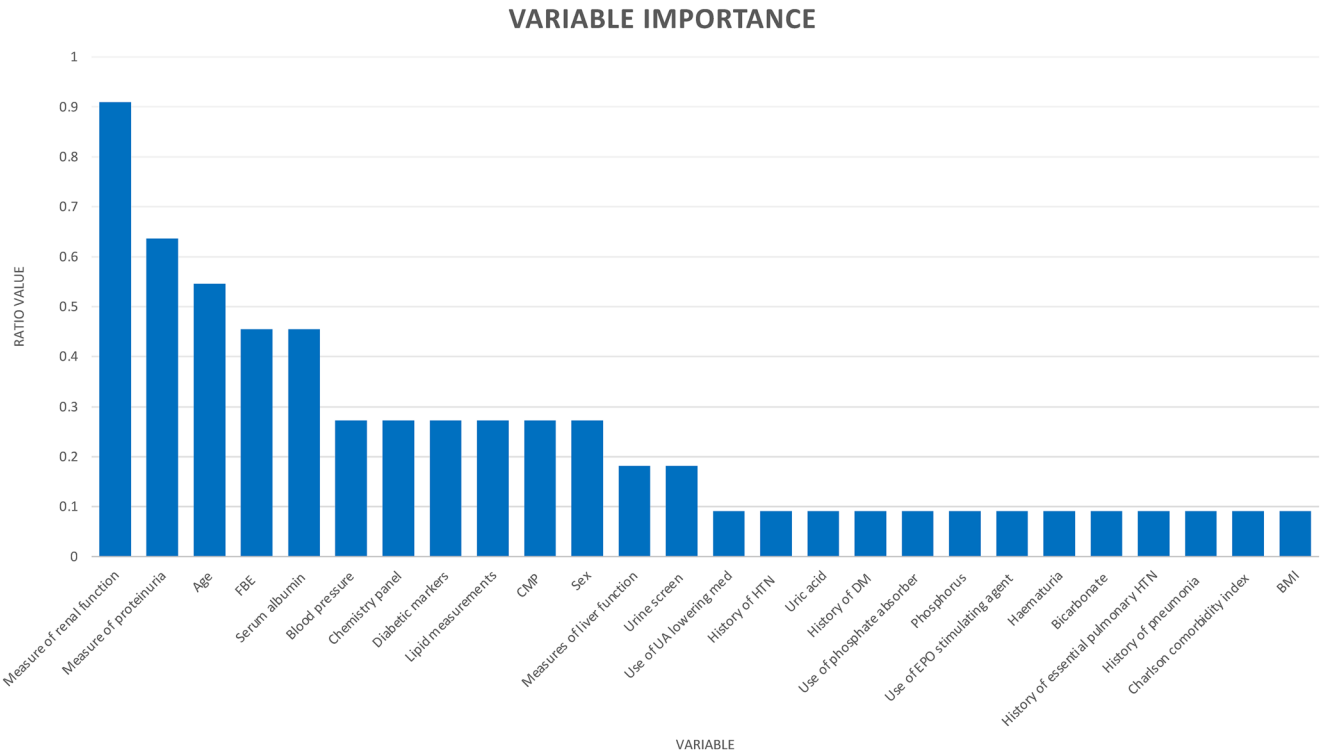

FIGURE 4 | Variable importance. Ratio of occurrence within top five most important variables to number of studies reporting variable importance. *FBE*; full blood examination, *CMP*; calcium magnesium phosphate, *UA*; uric acid, *HTN*; hypertension, *DM*; diabetes mellitus, *EPO*; erythropoietin, *BMI*; body mass index.

These data form the foundation for future predictive models to be built upon.

This paper includes several limitations. Firstly, this paper is a narrative review. As such only one author was involved in the selection of studies and no assessment of bias was performed. Furthermore, while ML technicalities were not required for this study, the author is not trained in ML and AI. Thus, some of the language of this subject may not be accurately represented in this review. Non-English language papers were excluded from this study. As the majority of the included papers come from non-English speaking countries (13 of the 16 studies), key literature may have been missed. Finally, variables were grouped into overall categories such as 'measures of renal function' containing eGFR and serum creatinine. These groupings contain inherent assumptions based upon clinical experience within the Australian healthcare system and may not reflect international practices.

4.4 | Future Directions

The findings of this study support ML as a viable method to predict CKD progression to KF. This review forms the foundation for the development of a ML model utilising the variables of importance identified within the literature. Such a model could serve to optimise the referral pathway of CKD patients to nephrology services for those individual at greatest risk of progressive disease. Future research should seek to determine how ML predative capabilities compare to models such as KD Predict with the integration of competing risks.

5 | Conclusion

The aim of this review was to identify the most common and important variables (demographic, clinical and biochemical) used in ML models to predict the progression of CKD to KF. Despite great variation, key variables emerged in both the frequency of usage as well as the importance to model prediction. The majority of the identified variables support the current clinical understanding of CKD, however, several variables such as measures of liver function and serum albumin outperformed clinical expectations and may warrant inclusion in any future ML models. These findings lay the foundations for the development and validation of a ML model capable of rivalling the KFRE in the provision of accurate KF prediction for clinicians to prioritise those who are most at risk.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Appendix A

Search Strategies

Ovid MEDLINE January 2017 to 5th of August 2023

1.	exp Renal Insufficiency, Chronic/
2.	"chronic kidney disease".ti,ab,kf.
3.	"chronic kidney failure".ti,ab,kf.
4.	"chronic renal failure".ti,ab,kf.
5.	("CKD" or "CRD" or "CRF" or "CKF"). ti,ab,kf.
6.	1 or 2 or 3 or 4 or 5
7.	exp Artificial Intelligence/
8.	exp Machine Learning/
9.	"deep learning".ti,ab,kf.
10.	"neural network".ti,ab,kf.
11.	"computational$".ti,ab,kf.
12.	7 or 8 or 9 or 10 or 11
13.	"end stage renal disease".ti,ab,kf.
14.	"end stage kidney disease".ti,ab,kf.
15.	"end stage renal failure".ti,ab,kf.
16.	"end stage kidney failure".ti,ab,kf.
17.	("ESRD" or "ESKD" or "ESRF" or "ESKF").ti,ab,kf.
18.	"dialy$".ti,ab,kf.
19.	("GFR" or "glomerular filtration rate"). ti,ab,kf.
20.	13 or 14 or 15 or 16 or 17 or 18 or 19
21.	6 and 12 and 20
22.	limit 21 to yr="2017 -Current"

Ovid EMBASE January 2017 to 5th of August 2023

1.	exp chronic kidney failure/
2.	"chronic kidney disease".ti,ab,kf.
3.	"chronic renal failure".ti,ab,kf.
4.	"chronic renal insufficiency".ti,ab,kf.
5.	("CKD" or "CRD" or "CKF" or "CRF").ti,ab,kf.
6.	1 or 2 or 3 or 4 or 5
7.	exp artificial intelligence/
8.	exp machine learning/
9.	"deep learning".ti,ab,kf.
10.	"neural network".ti,ab,kf.
11.	"computational$".ti,ab,kf.
12.	7 or 8 or 9 or 10 or 11
13.	exp end stage renal disease/
14.	"end stage kidney disease".ti,ab,kf.
15.	"end stage renal failure".ti,ab,kf.
16.	"end stage kidney failure".ti,ab,kf.
17.	("ESKD" or "ESRD" or "ESKF" or "ESRF"). ti,ab,kf.
18.	"dialy$".ti,ab,kf.
19.	("GFR" or "glomerular filtration rate").ti,ab,kf.
20.	13 or 14 or 15 or 16 or 17 or 18 or 19
21.	6 and 12 and 20
22.	limit 21 to yr="2017 -Current"