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Comparison of Chronic Kidney Disease Unknown Etiology (CKDu) Prevalence in Industrial Workforce Using Different eGFR Equations

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Abstract

Background: Industrial workers are vulnerable to the development of kidney disease owing to the associated risk factors and work-related fatigue. It is essential to compare the prevalence of CKDu among workers using different (eGFR) equations. This study aims to evaluate prevalence of CKDu among industrial workers and compare using different eGFR equations.
Materials and Methods: A cross-sectional study was conducted on 132 industrial workers (91 men and 41 women). Serum creatinine was analysed and eGFR values were calculated based on the modification of diet in renal disease-175 (MDRD-175), MDRD-186, Cockcroft Gault (CG), and chronic kidney disease-epidemiology collaboration (CKD-EPI) equations. CKDu stages were ascertained using KDIGO guidelines.
Results: Average age and BMI of the workers were 33.5 years and 24 kg/m2, respectively. Mean serum creatinine level was 1.0 (0.3–1.8) mg/dL. The CKD-EPI equation revealed highest mean eGFR value followed by CG, MDRD-186, and MDRD-175. CKDu prevalence among workers was 9.1% with MDRD-175, 4.6% as per MDRD-186, 9.9% in CG, and 3.1% as per CKD-EPI equations. Notably, the mean creatinine and eGFR values were lower in female workers when compared to males. Further, the prevalence of CKDu stage 2 was higher in females, while stage 3 (eGFR < 60 mL/min/m²) was significantly more prevalent among males than females.
Conclusion: The prevalence of CKDu was found to be significantly higher among male than female workers. The rates of CKDu determined using MDRD-186 and CKD-EPI equations were comparable and can be used to predict the CKDu prevalence among industrial workers from different occupational settings.

Keywords: Chronic Kidney Disease of Unknown Etiology, Workers, Glomerular Filtration Rate

Introduction

Chronic kidney disease of unknown etiology (CKDu) is a global health concern and an independent risk factor for all-cause mortality, particularly for cardiovascular disease. Various risk factors such as age, sex and personal habits including smoking and alcohol consumption, independently influence the development of CKDu [1]. However, recent scientific findings have emphasized that the occupational exposures to heat stress [2], agrochemicals [3], heavy metals and organic compounds [4] show promising association with CKDu. Exposure to particulate matter in occupational settings is one of the risk factors for increase in CKDu [5]. The activation of oxidative stress, inflammation pathways, impairments of DNA repair mechanisms, endoplasmic reticulum stress, as well as changes in mitochondrial DNA are also contributors to CKDu development. In addition to above factors, exposure to dioxins, bisphenol A, phthalates and BFAs induces proteinuria, affecting the glomeruli and renal tubules [6]. Note that CKDu is silent killer and early diagnosis can delay or prevent progression of CKDu [7].

Equations of estimated glomerular filtration rate (eGFR) are widely utilized to identify chronic kidney disease risk. These equations are based on age, gender, race, and serum creatinine levels [8]. The most commonly used equations include Cockcroft Gault (CG), Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease (MDRD)-186 and MDRD-175, a revised form of traditional MDRD-186 equation with low biased to estimate eGFR values using serum creatinine and physical characteristics of age, sex and race [9]. The majority of epidemiological studies employ Kidney Disease Improving Global Outcomes (KDIGO) guidelines to determine the prevalence of CKD, which is based on the glomerular filtration rate [10].

In the general population, the prevalence of CKD is reported within the range from 1 to 13% and it is evaluated using an eGFR value of lower than 60 ml/min per 1.73 m² [11]. Similarly, the prevalence of CKDu has been compared using different eGFR equations in various population studies in post cardiovascular surgery patients [9], the adult population in Japan [12], China [13], Pakistan [14], individuals with T2DM [15], the elderly population [16], and those with heart failures [17].

In occupational research, countless studies have observed altered renal functions among workers exposed to heavy metals and organic compounds [18-21]. However, few studies have specifically analyzed the risk of exposure in relation to CKDu. In addition, industrial workers have indicated a higher prevalence of occupational stress [22], cardiovascular diseases [23], overweight or obesity [24], hypertension [25], as well as poor sleep quality and work-related fatigue [26]. These problems may influence the development of CKDu in industrial workforce. A study by Lan et al., (2023) reported that increased working hours are risk factor for developing CKD [27]. A recent study found lower eGFR and a higher odds ratio of risk factors [28]. Meanwhile, some studies have raised concerns about clinically relevant differences observed in GFR estimation equations [29,30]. Thus, the present study aimed to assess and compare the prevalence of CKDu in the industrial workforce using different eGFR equations.

Materials and Methods

The study included 132 industrial workers consisting of 91 men and 41 women, who were employed in manufacturing operations i.e. bearing and flavors units located in Karnataka. India. This study found that workers in bearing industries are exposed to metals and emulsified oils either directly or indirectly through aerosols [31]. Similarly, the workers from flavors industry are exposed to volatile organic compounds along the process [32]. Thus, workers from these industries have been included in the current study. The convenience sampling method was adopted for subject recruitment. The study protocol was approved by the Institutional Ethical Committee (IEC) under sanction number 2, dated 13-12-2018, which works in accordance with the National Ethical Guidelines in India. Prior to their participation, the subjects were informed about the study objectives and their consent was obtained. The subjects who were above 18 years of age, had a minimum of 2 years of experience and willing to participate in the study were included, while those suffering from major health disorders and under medication for long term were excluded.

A pre-structured survey form was applied to collect the details on age, gender, height (in centimeters), and weight (kilograms) to calculate BMI (kg/m2). The current study did not include the data on work history and family history which are risk factors influencing the e-GFR values. In our previous study, the presence of risk factors and prevalence of CKDu among these workers showed no significant differences [28].

One mL of whole blood sample was collected in plain tubes, with serum samples separated using 4000 RPM for ten minutes at 4◦C. The separated serum was employed for the analysis of creatinine. The modified kinetic Jaffe method was utilized for the analysis of serum creatinine.

Estimated glomerular filtration rate (eGFR): The eGFR values were calculated using four different equations as described earlier [9]. These equations are derived based on the inputs of age, gender, weight, and serum creatinine. The details of eGFR equations used in this study are described below.

Formula 1.

$$MDRD186 = 186 \times s^{Cr-1.154} \times age^{-0.203} \times (0.742\ if\ female)$$

$$MDRD186 = 175 \times s^{Cr-1.154} \times age^{-0.203} \times (0.742\ if\ female)$$

$$CG = [(140 - age) \times \frac{Weight}{72 \times s^{Cr}} \times (0.85\ if\ female)]$$

$$\begin{aligned} CKD = & if\ SCr < 0.9\ (for\ male): 141 \times \frac{SCr}{0.9} - 0.411 \times 0.993^{Age} \\ & if\ SCr < 0.9\ (for\ male): 141 \times \frac{SCr}{0.9} - 1.209 \times 0.993^{Age} \\ & if\ SCr < 0.7\ (for\ male): 144 \times \frac{SCr}{0.7} - 0.329 \times 0.993^{Age} \\ & if\ SCr < 0.7\ (for\ male): 144 \times \frac{SCr}{0.9} - 1.209 \times 0.993^{Age} \end{aligned}$$

The different stages of chronic kidney disease of undetermined cause (CKDu) are classified according to the KDIGO guidelines. The stages are categorized as normal (stage 1), mild (stage 2), moderate (stage 3), severe (stage 4), and kidney failure (stage 5), corresponding to estimated Glomerular Filtration Rate (eGFR) values of ≥ 90, 89-60, 59-30, 29-15, and <15 ml/min per 1.73 m2 respectively. eGFR values lower than 60 ml/min per 1.73 m2 represent the presence of CKDu.

Data analysis was performed using SPSS version 23 software. The details of age, BMI, serum creatinine, and eGFR values obtained from different eGFR equations among industrial workers were presented as mean ± SD, minimum and maximum. The demographic details such as serum creatinine and eGFR values were compared between gender (male and female) and age category through the student t test. The prevalence of CKDu stages (1 to 3) between male and female workers was also compared using the chi-square test. The correlation between eGFR values derived from different eGFR equations was evaluated using Pearson correlation coefficient test. Statistical significance is defined as a P value less than 0.05.

Results

The data regarding the age, BMI, serum creatinine, and eGFR value in different equation among industrial workers are provided in Table 1. The average age of the workers was 33.5 years, and their mean BMI was 24 kg/m². The mean eGFR values calculated using different equations for the workers were found to be 95, 89.4, 97.5, and 101.7 for the MDRD-186, MDRD-175, CG, and CKD-EPI equations, respectively. The eGFR values obtained from different equations were found to be comparable.

Table 1. Details of age, body mass index, and eGFR values among industrial workers

Variables	Mean ± SD n = 132	Min	Max
Age (years)	33.5± 9.6	19.0	68.0
Body mass index (Kg/m^2)	24.0 ± 4.0	16.4	40.4
Serum creatinine (mg/dL)	1.0 ± 0.3	0.3	1.8
MDRD-186 (mL/min/1.73m^2)	95.0± 42.1	48.0	372.0
MDRD-175 (mL/min/1.73m^2)	89.4± 39.6	45.0	350.0
CG (mL/min/1.73m^2)	97.5± 41.5	48.0	329.0
CKD-EPI (mL/min/1.73m^2)	101.7± 23.3	50.0	183.0

MDRD: Modification of diet in renal disease, CG: Cockcroft and Gault, CKD-EPI: Chronic kidney disease epidemiology collaboration,

Table 2 compares age, BMI, serum creatinine, and eGFR values between male and female workers. The age and BMI of male and female workers were found to be comparable. Nevertheless, female workers had significantly lower mean serum creatinine (0.9 vs 1.0 in males) and eGFR values as estimated by MDRD-186, MDRD-175, and CG equations in comparison to their male counterparts. In contrast, the mean eGFR values obtained from the CKD-EPI equation were significantly higher in females than in males.

Table 2. Comparison of demographic, serum creatinine, and eGFR values between male and female workers

Variables	Gender Mean ± SD		P-value
	Male (n=91)	Female (n=41)	
Age (years)	33.9 ± 10.1	32.5 ± 8.5	0.410
Body mass index (Kg/m^2)	23.8 ± 3.5	24.6 ± 5.1	0.252
Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	**0.001**
MDRD -186 (mL/min/1.73 m^2)	99.5 ± 46.1	85.2 ± 29.4	**0.034**
MDRD - 175 (mL/min/1.73 m^2)	93.6 ± 43.5	80.2 ± 27.6	**0.035**
CG (mL/min/1.73 m^2)	102.7 ± 45.2	85.9 ± 29.0	**0.012**
CKD - EPI (mL/min/1.73 m^2)	95.8 ± 24.2	114.7 ± 14.3	**0.001**

eGFR: Estimated glomerular filtration rate, MDRD: Modification of diet in renal disease, CG: Cockcroft and Gault, CKD-EPI: Chronic kidney disease epidemiology collaboration.

Table 3 outlines data regarding serum creatinine and eGFR values among industrial workers, based on age distribution i.e. >40 and <40. Workers in the category of >40 years revealed elevated serum creatinine levels and diminished eGFR values. However, a significant difference was noted in CG equation.

Table 3. Comparison of serum creatinine and eGFR values in workers according to age category

Variables	Age (years) category Mean ± SD		P-value
	< 40 (n=106)	>40 (n=26)	
Creatinine (mg/dL)	1.0 ± 0.3	1.0 ± 0.2	0.795
MDRD-186 (mL/min/1.73m^2)	96.7± 44.4	88.1 ± 30.7	0.355
MDRD- 175 (mL/min/1.73m^2)	91.0± 41.8	82.9± 29.0	0.354
CG (mL/min/1.73m^2)	100.8± 43.4	83.8± 29.3	**0.020**
CKD-EPI (mL/min/1.73m^2)	101.7 ± 22.6	101.4± 26.4	0.942

eGFR: estimated glomerular filtration rate, MDRD: Modification of diet in renal disease, CG: Cockcroft and Gault, CKD-EPI: chronic kidney disease epidemiology collaboration

According to eGFR values obtained from the different equations, the subjects were classified into different CKDu stages as per KDIGO guidelines (Table 4). The prevalence of CKDu stages among workers as per MDRD-186 equation was found as 43.9% (stage 1), 51.5% (stage 2), and 4.6% (stage 3), respectively. In the MDRD-175 equation, it was noted as 31.1% (stage 1), 59.8% (stage 2), and 9.1% (stage 3), respectively. The comparison of CKDu stages between male and female workers derived from the MDRD-186 and MDRD-175 equations was found significant, whereby CKDu stage 2 was noted higher among female than male workers. The prevalence of CKDu stages as per the CG equation was 47.7% (stage 1), 42.4% (stage 2), and 9.9% (stage 3), respectively. The comparison of CKDu stages between male and female workers was found to be non-significant. The prevalence of CKDu stages as per CKD-EPI equation was 72.7% (stage 1), 24.2% (stage 2), and 3.1% (stage 3), respectively. The difference in CKDu stages between male and female workers was found significant. In all eGFR values, except for CG equation, the prevalence of CKDu stage 3 (60 ml/min per 1.73 m2) was higher in male workers as compared to female workers.

Table 4. Prevalence of CKDu stages among male and female industrial workers

Variables	CKDu stage	Gender: Male n	Male %	Female n	Female %	Total n	Total %	Chi-square	P-value
MDRD-186	1	49	53.8	09	22	58	43.9	13.82	0.001
	2	37	40.7	31	75.6	68	51.5		
	3	05	5.5	01	2.4	06	4.6		
MDRD-175	1	35	38.5	06	14.6	41	31.1	10.56	0.005
	2	46	50.5	33	80.5	79	59.8		
	3	10	11	02	4.9	12	9.1		
CG	1	49	53.8	14	34.1	63	47.7	4.76	0.092
	2	35	38.5	21	51.3	56	42.4		
	3	07	7.7	06	14.6	13	9.9		
CKD-EPI	1	56	61.5	40	97.6	96	72.7	18.50	0.001
	2	31	34.1	01	2.4	32	24.2		
	3	04	4.4	00	0.0	04	3.1		

CKD stage 1: >90 ml/min per 1.73 m2, CKDu stage 2: 89-60 ml/min per 1.73 m2 and CKDu stage 3: <60 ml/min per 1.73 m2
CKDu: Chronic kidney disease of unknown etiology, MDRD: Modification of diet in renal disease, CG: Cockcroft and Gault, CKD-EPI: Chronic kidney disease epidemiology collaboration.

Table 5 reports the correlation between eGFR values obtained from different equations. The association between MDRD-186 and MDRD-175, CG, and CKD-EPI was positive and significant. The highest correlation was noted between MDRD-186 and MDRD-175 followed by CG and CKD-EPI.

Table 5. Correlations coefficient between eGFR values derived from different equations

Variables	MDRD-186	MDRD-175	CG	CKD- EPI
MDRD-186	1.000	-	-	-
MDRD- 175	1.000**	1.000	-	-
CG	0.883**	0.882**	1.000	-
CKD- EPI	0.251**	0.252**	0.206*	1.000

CKDu: chronic kidney disease of unknown etiology, MDRD: Modification of diet in renal disease, CG: Cockcroft and Gault, CKD-EPI: chronic kidney disease epidemiology collaboration.

Fig. 1A displays a scatter plot of eGFR values between the MDRD-186 and MDRD-175 equations, where R square was noted as 1.000. eGFR values derived from these equations were found close to each other. Figure 1B displays the scatter plot of eGFR values between MDRD-186 and CG, with R2 found to be 0.780. Figure 1C indicates the scatter plot eGFR values between MDRD-186 and CKD-EPI and found lower association (R2 = 0.006). Also, Figure 1D depicts scatter plot of eGFR values between CG and CKD-EPI equation where R2 was found to be 0.043. Figure 1E is a scatter plot of the eGFR values between MDRD-175 and CG, and was found to be 0.778. Finally, Figure 1F is a scatter plot of eGFR values between MDRD-175 and CKD-EPI, with R2 found to be 0.063.

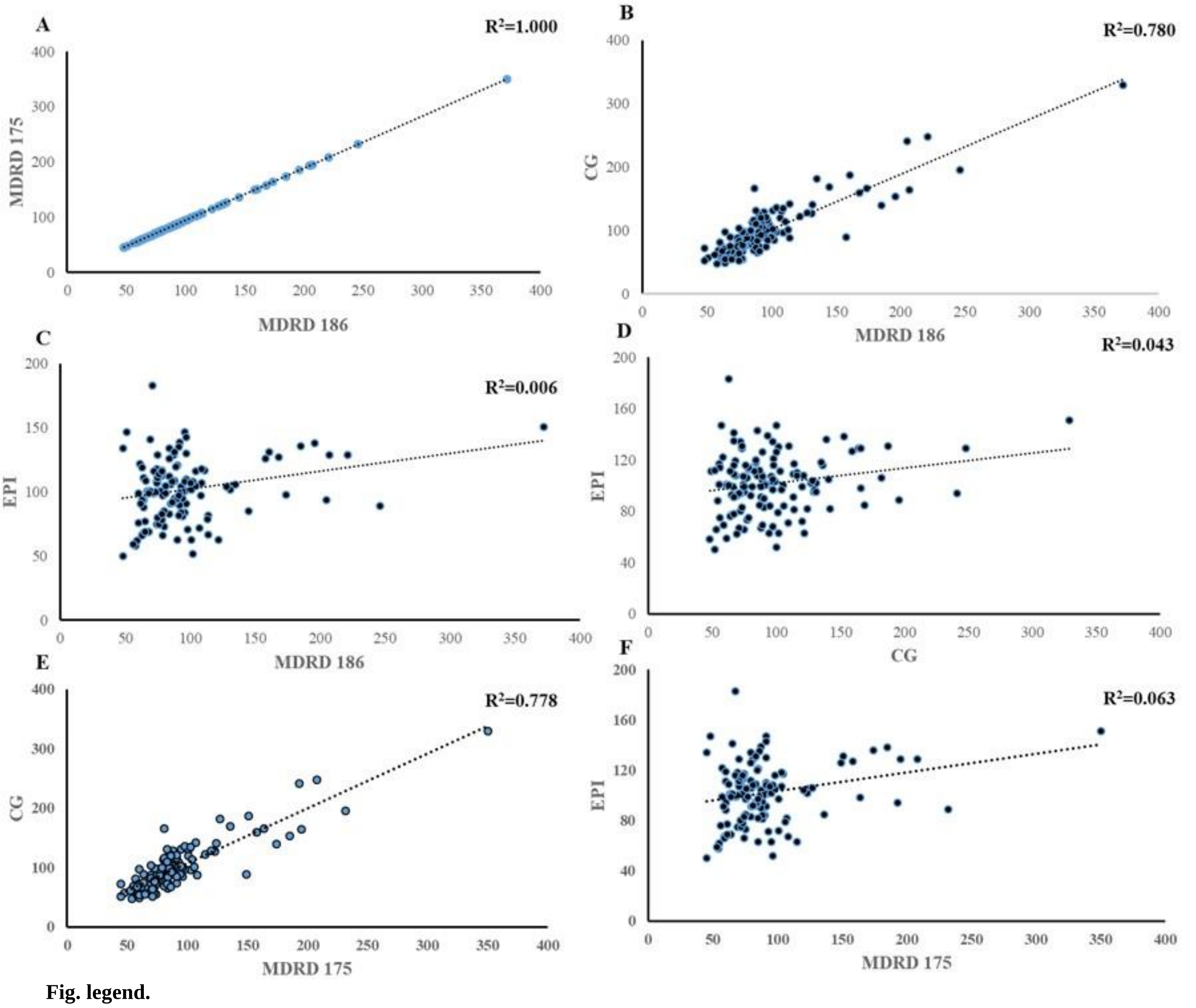

Fig. legend.
Fig. 1A. Represents the scatter plot of eGFR values between MDRD-186 and MDRD -175 equations.
Fig. 1B. Presents the scatter plot of eGFR values between MDRD-186 and CG equations.
Fig. 1C. Represents the scatter plot of eGFR values between MDRD-186 and CKD-EPI equations.
Fig. 1D. Represents the scatter plot of eGFR values between CKD-EPI and CG equations.
Fig. 1E. Depicts the scatter plot of eGFR values between MDRD-175 and CG equations.
Fig. 1F. Depicts the scatter plot of eGFR values between MDRD-175 and CKD-EPI equations.

Discussion

The CKDu is a global silent killer imposing a huge burden on the world health economy. Occupational exposure is one of the risk factors for the development of CKDu [18]. Although many studies have analyzed kidney functions among workers exposed to different occupational exposure [33, 34], very few studies have measured the risk for the development of CKDu. Thus, the current study determined the prevalence of CKDu among industrial workers working in the bearing and flavors manufacturing industry. The CKDu prevalence among workers were analyzed based on KDIGO guidelines, which are widely used in occupational [35] and general population-based studies [36, 37]. The KDIGO 2012 guidelines recommend classifying patients based on their GFR values to predict the prognosis of chronic kidney disease (CKD) [38]. Various equations, such as MDRD-175, MDRD-185, CKD-EPI, and CG have been used to calculate eGFR values in various populations, including cardiovascular surgery patients [9], Japanese adults [12], and Chinese populations [13]. Thus, in this study, we utilized these equations to analyze the prevalence of CKDu among the working population.

In these equations, serum creatinine levels of individuals were used to calculate eGFR values as described [8, 9]. Our findings indicated that the mean serum creatinine level was 1.0 mg/dL, with a range of

0.3 to 1.8 mg/dL. Similar serum creatinine levels have been observed in workers from paint factories, tile industries, gas and petrol stations, and tanneries [19, 39-41]. Notably, we found significantly higher serum creatinine levels in male workers when compared to female workers, a trend also observed in elderly population [16]. The average eGFR values for workers derived from various equations were as follows: MDRD-186: 95.0 mL/min/1.73 m², MDRD-175: 89.4 mL/min/1.73 m², Cockcroft-Gault (CG): 97.5 mL/min/1.73 m², and CKD-EPI: 101.7 mL/min/1.73 m². These outcomes were comparable to patients who had undergone cardiovascular surgery [9], kidney transplant [42], lead workers using MDRD-186 equation [43], and migrant farm workers using the CKD-EPI equation [44]. Various factors including age, gender, BMI, and duration of work significantly affect the eGFR estimation [45, 46]. Thus, all SCr-based eGFR equations can be regarded as gender/race/age-adjusted SCr [47]. However, studies suggest that age and gender are important factors determining normal GFR in living kidney donors [48], while age, sex, and race are found to be less influence on prevalence of CKD among acute kidney injury patients [49]. Data from a systematic review clearly revealed that with every 10-year increase in age, the chance of occurrence of CKDu increased where age of over 40 years was more associated with CKDu [50]. Thus, in this study, we analyzed the influence of gender (male vs. female) and age (<40 vs. >40 years) on eGFR values among workers, using different equations. The mean eGFR values for males were found to be lower than those for females. Further, age category appeared to have a limited impact on eGFR outcomes among workers. Similar findings were reported by Poggio et al. (2009), where females exhibited slightly higher measured GFR (mGFR) than males after adjusting for body surface area [48]. Nevertheless, it should be noted that donors over 45 years of age experience a significant decline in GFR values compared to younger donors. While the average age of our study group was 33.5± 9.6, this might be the one of the reasons for age as to have less of an impact on CKDu outcomes.

In the current study, we estimated the prevalence of CKDu (<60 mL/min/1.73 m²) among industrial workers using different equation. It was found to be 4.6%, 9.1%, 9.9%, and 3.1% with MDRD-186, MDRD-175, CG, and CKD-EPI respectively. The study among male workers from sugarcane, corn, plantain cultivation, brick making, and construction indicated the prevalence of 7.4% as per CKD-EPI equation [35]. In this study, we noted 3.1% in both male and female workers. Similarly, study by Ekiti et al., 2018 indicated similar prevalence in sugarcane workers as per CKD-EPI equation [51]. Delaney et al. examined CKDu prevalence in the general population with a mean age of 61 years using MDRD-175 and CKD-EPI equations [52] and found CKDu prevalence to be 11% in MDRD-175 and 8% in the CKD-EPI equations. Cepni et al. reported a prevalence of 16.8% in MDRD-175 and 20% in the CKD-EPI equation in elderly pre-operative patients [16]. In our study, we found the prevalence to be 9.1% and 3.1%, respectively. We noted a lower CKDu prevalence, which may be attributed to the age difference between the previous and current study. Alemu et al. observed 17.3% using MDRD and 14.3% based on CKD-EPI equations in diabetic patients [53]. In our current study, we observed a lower CKDu prevalence in industrial workers compared to the diabetic patient data. Matsushita et al. observed a low prevalence of CKDu using the CKD-EPI equation compared to MDRD equations [54]. In our study, we also found a lower CKDu prevalence in the CKD-EPI equation compared to MDRD-186, MDRD-175, and CG equations.

In the current study, we observed a higher prevalence of CKDu stage 2 among the female workforce when compared with males. This trend was observed in MDRD-186, MDRD-175, and CG equations. A similar trend was noticed in other studies [55, 56]. However, the majority of the equations predicted higher prevalence of CKDu stage 3 (< 60mL/min/m2) among male workers than females and similar type of result was noticed by Raines et al., 2014, where prevalence of CKDu among male workers is four times higher than females [57]. Similar observations were noticed by Abeywickrama et al., 2020, and concluded that males show higher prevalence of CKDu than females [58]. A systematic review on factors associated with CKDu concluded male gender as a predisposing factor for CKDu and hence males are more affected than their female counterparts [50].

Based on the study outcomes, it can be interpreted that industrial workers are at higher risk of developing CKDu. Nevertheless, the result should be interpreted cautiously as authors did not collect the family history of the workers during sample collection. The study also further calls for a similar type of study among various occupational settings on a larger scale among industrial workers, while considering relevant risk factors.

Conclusion

The serum creatinine and eGFR values were significantly lower in female workers when compared to male workers. The CKD-EPI-derived equation revealed the highest mean eGFR value followed by CG, MDRD-186, and MDRD-175. The prevalence of CKDu (stage 3) was higher in the CG-derived equation followed by MDRD-175, MDRD-186, and CKD-EPI equations. CKDu (stage 3) was more prevalent in male workers than among female counterparts. The prevalence of CKDu derived from CG and MDRD-175 equation was comparable, while the prevalence from MDRD-186 and

CKD-EPI was also similar. Industrial workers are at higher risk of developing CKDu, and regular screening for serum creatinine is recommended to lower the prevalence of CKDu among such workers. It is also suggested to conduct a similar type of study among various occupational settings, taking into account relevant risk factors.

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Conflict of interest

None declared.

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Ethical Considerations

This research was carried out as per the ethical guidelines which works in accordance with the National Ethical Guidelines in India (ICMR). Prior to their participation, the subjects were informed about the study objectives and their consent was obtained.

Code of Ethics

The study protocol was approved by the Institutional Ethical Committee (IEC) under sanction number 2, dated 13-12-2018.

Authors' Contributions

Raju Nagaraju: Data collection, Biochemical Analysis, Methodology, and Drafting of the manuscript; Kalahasthi Ravibabu: Conceptualization, Supervision of the work, data analysis, and editing of the manuscript; Surendar Jakkam : data analysis and editing of the manuscript; Ravi Prakash Jamalpur: Data collection and Biochemical Analysis; Vinay Kumar Adepu: Data collection, Biochemical Analysis, and editing of the manuscript.

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