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A Retrospective Combination Health Outcomes Study among Diabetic Patients with Chronic Kidney Disease: A Multi-Level Study

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Abstract

Diabetes is the prominent cause of the progression of chronic kidney diseases (CKD) worldwide. Effective implementation of healthcare services and healthcare delivery system to control glycemic level and slow annually declining eGFR remain a challenge in many countries including Thailand. The aims of this study were to investigate the association between individual and health service delivery factors on the combination health outcomes. This multi-level study applied case-control method was conducted. The 397 participants were recruited from 11 hospitals during December 2018 to May 2019 in Thailand. The samples were categorized into 4-group combination health outcome. Data analysis was performed by descriptive analysis and multi-level multinomial logistic regression analysis. The multinomial logistic regression in bivariate analysis showed that diabetes self-care activities score were more likely to control glycemic and CKD progression compared with those with a low-level of DSCA (OR 3.47; 95 % CI: 1.19 - 10.15). The rational drug uses (RDU) as the health service-level factors increased combination health outcomes 2 times (OR 2.41; 95 % CI: 1.05 - 5.53). The multi-level analysis found that performing with high-level of DSCA (OR 5.36; 95 % CI :1.99 - 14.46) and rational drug uses of metformin and NSAIDs (OR 2.33; 95 % CI: 1.25 - 4.36) increased probability to achieve combination health outcomes. Findings highlight the importance of diabetes self-care activities and health service delivery system to optimize the combination health outcomes among diabetic patients with CKD.

Keywords: Glycemic control, Chronic kidney disease progression, Integrated care, Diabetes selfcare activities, Multi-level

Introduction

The number of diabetes and diabetic nephropathy (DN) are increasing worldwide. The prevalence of diabetic kidney disease ranged between 15.4 to 53 % [1-3]. The prevalence of CKD among diabetes patients in Thailand was 24.4 % [4] but it was the global highest increase of diabetes-related ESRD incidence by 1,448 % during 2001 - 2015 that eventually required ongoing dialysis [2,5,6].

The glycemic control and slow kidney disease progression can decrease rate of diabetic retinopathy, nephropathy and cardiovascular diseases [7]. Although many interventions and clinical practice guidelines were established such as the organization Kidney Disease: Improving Global Outcomes (KDIGO) guideline management, the combination health outcomes of both HbA1C $\leq$ 7 % and annually declining eGFR $\leq$ 4 mL/min/1.73 m^2 could not achieve [8,9]. In Thailand, only 28.82 % were glycemic controllable and 64.2 % achieved CKD target [10].

Given patient factors, an advance age and obesity increased risk of nephropathy and diabetic kidney disease [11-13]. Diabetic nephropathy patient had 7 times to develop ESRD [14]. The diabetic patient showed the short median times of CKD progression about 5 to 8 years for changing GFR category [15]. Among type 2 diabetes with comorbid hypertension, CKD or CVD were found the increase of severe hypoglycemic events and all causes mortality rate [12,16]. Self-care activities presenting with adherence to medication and life style modification showed the beneficial evidences [17,18]. Besides the health service-level factors, despite increasing access to care by universal coverage in Thailand, the majority could not achieve the combination health outcomes [19]. Non-guideline concordance or irrational drug use (IRDU) of metformin indicated less glycemic control than RDU [20]. The existing care models were unclear and expressed specialist inaccessibility with care fragmentation [8,22-26]. The traditional and nonconventional

diabetes care strategies included community-based care in primary care, interdisciplinary care, nurse-led clinic and codesigned integrated care attempted to support these problems conducted by screening, providing education and self-management support. Although nurse-led care in community-based care had positive effects on specific clinical outcomes such blood pressure, lipid, glycemic and renal progression, most previous studies were short in duration and low participant number [27]. Considering with health-related quality of life, the codesigned integrated care for diabetes and CKD stage 3a and above could not indicate the significant outcomes [28]. Developing the program or care model for these comorbidities should meet the patient needs and feasibility. The complexity of comorbidities may attribute to multifactorial and interaction factors of patient health service system. There were few studies have investigated the combination health outcomes in the multivariate and multi-level study.

We hypothesized that the patient-level factors consisted of age, BMI, co-morbidity and diabetes self-care activities; the health service-level factors consisted of model of care, perceived integrated care, rational drug uses (RDU) and crowding were associated with the combination health outcomes. The aim of the study was to investigate the association between patient-level and health service-level factors on combination health outcomes namely glycemic control and chronic kidney disease progression. In addition, we focused on the multi-level analysis to find the appropriate model for diabetic patients with CKD in Thailand.

Materials and methods

This study was an analytical epidemiological study applying the case-control method. The sample size was calculated by Fleiss method without adjusted correction factors. The ratio of case to control was 70:30 or approximate 2:1 related to glycemic control rate in Thailand [20]. After approval from the Ethics Committee of the Faculty of Medicine, Siriraj Hospital, Mahidol University (Si 263/2018), BMA Human Research Committee (BMAHREC), Chonburi Research Hospital Center (1620032562) and other 8 hospital-settings, the study was conducted. The multi-stage random sampling of population was applied at the first-level of health service area and the second-level of hospital setting. The random sampling hospitals consisted of primary, secondary and tertiary hospitals. The probability proportional to size (PPS) was performed to estimate sample size in 11 hospital settings. In each hospital setting, the samples who met the inclusion criteria were selected (**Figure 1**). The outcome interest in this study were the combination health outcomes classified into 4 groups. Regarding to multi-level study, the independent variables consisted of patient and health service-level factors. The patient-level factors were age, BMI, Charlson comorbidity index (CCI) and diabetes self-care activity score (DSCA) [29-31]. The patient-level factors were the model of care, perceived integrated care, rational drug use and crowding.

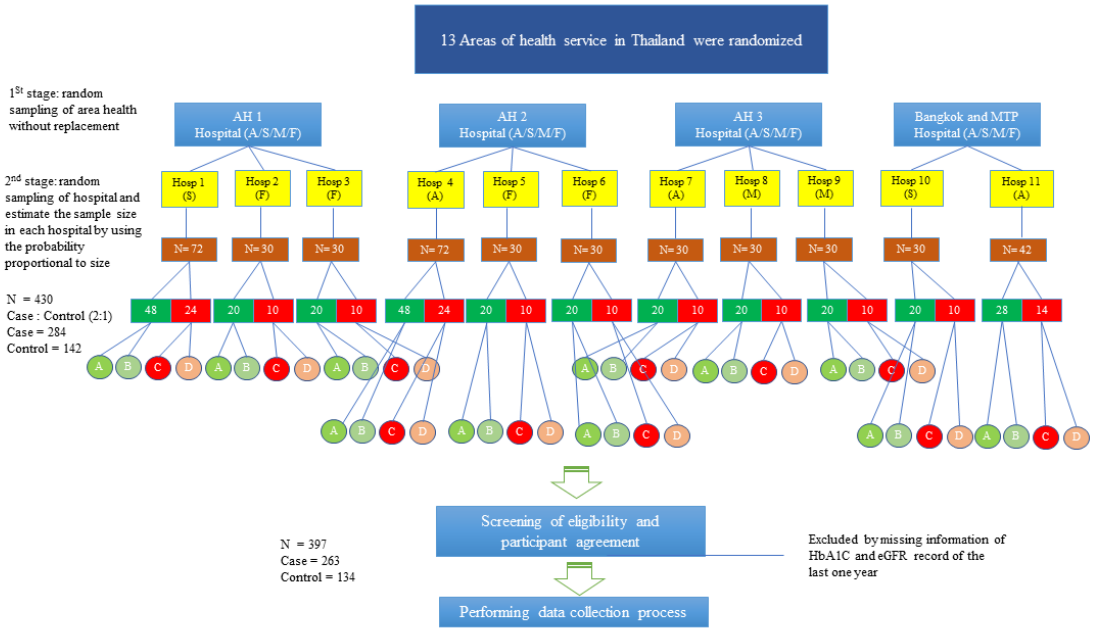

Figure 1 The multi-stage random sampling of a probability sample of diabetic patients with CKD

Descriptive statistic was performed to assess the demographic and clinical characteristics. Continuous variables were described by mean and standard deviation (SD). The multinomial logistic regression (MLR) was conducted to examine the association between the patient-level and health service-level on combination health outcomes [32]. A reference category was the uncontrolled DM and rapidly declined eGFR group (group A). The report of exponential generated the odd ratio for comparing the occurrence of outcome of interests compared with the reference group. The best outcome was the controlled DM and slowly declined eGFR group. The likelihood-ratio test (LR test) was used to evaluate the overall effects of each predicted variable.

The multi-level MLR was used to examine the combination health outcomes which nested into health service-level. For assumption testing, the violation and multicollinearity test were not found. The researcher 2 model of M1, M2, M3 and the last model (M4) by adding covariate and variables from patient-level and health service-level to estimate the MLR for predicting glycemic control and CKD progression. Significant factors in univariate analysis were included in the model by stepwise procedure. Finally, the best model was selected based on -2 log likelihood (-2LL) criterion. All analyses were performed in STATA version 15 (Stata Corp, College Station, USA).

Results and discussion

A total of 397 participants were included with the mean age of 64.87 (SD7.75; range 39 - 75). Female constituted 68.26 % of the study population with 74.81 % elderly patients. They were diagnosed CKD stage 3a (44.58 %), 3b (41.81 %) and 4 (13.60 %). Diabetic retinopathy patients were observed in 16.88 %. Nearly eight percent of them suffered from peripheral neuropathy. The case-control group characteristics was presented in **Table 1**.

Table 1 Case-control group characteristics.

Characteristics	Overall	Case (Uncontrolled DM)		Control (Controlled DM)	
		A (Rapid)	B (Slow)	C (Rapid)	D (Slow)
HbA1C	7.82 ± 1.77	8.75 ± 1.70	8.55 ± 1.52	6.13 ± 0.61	6.24 ± 0.52
eGFR	42.27 ± 11.33	39.95 ±11.23	44.56 ± 10.74	41.50 ± 11.64	42.18 ± 11.71
Declining eGFR	4.21 ± 10.97	11.69 ± 7.67	–2.30 ± 6.49	14.41 ± 11.47	–2.23 ± 5.97
Comorbidity					
Mild	378 (95.21 %)	116 (96.67 %)	135 (94.41 %)	50 (92.59 %)	77 (96.25 %)
Moderate to severe	19 (4.79 %)	4 (3.33 %)	8 (5.59 %)	4 (7.41 %)	3 (3.75 %)
DSCA score	4.92 ± 0.96	4.80 ± 0.99	4.88 ± 0.99	5.03 ± 0.75	5.03 ± 0.75
BMI					
Underweight	10 (2.52 %)	4 (3.33 %)	4 (2.80 %)	1 (1.85 %)	1 (1.25 %)
Normal	158 (39.80 %)	47 (39.17 %)	54 (38.30 %)	23 (42.59 %)	34 (42.50 %)
Overweight	143 (36.02 %)	39 (32.50 %)	56 (39.72 %)	14 (25.93 %)	34 (42.50 %)
Obese	86 (21.66 %)	30 (25 %)	29 (20.28 %)	16 (29.63 %)	11 (13.75 %)
Perceived integrated care					
Low	190 (47.86 %)	57 (47.5 %)	68 (47.55 %)	21 (38.89 %)	44 (55.00 %)
Moderate	96 (24.18 %)	31 (25.38 %)	36 (25.17 %)	13 (24.07 %)	16 (20.00 %)
High	111 (27.96 %)	32 (26.67 %)	39 (27.77 %)	20 (37.04 %)	20 (25.00 %)
Rational drug uses	265 (66.75 %)	64 (53.33 %)	105 (73.43 %)	36 (66.67 %)	60 (75.00 %)
Crowded clinic	336 (84.63 %)	99 (82.50 %)	123 (86.01 %)	43 (79.63 %)	71 (88.75 %)

Analyzing by MLR, the high-level of self-care abilities accounted for the higher probability to achieve combination health outcomes compared with the low-level of DSCA in reference group (adjusted OR 3.47; 95 % CI: 1.19, 10.15). For health service-level, the rational drug uses also demonstrated the positive effect on combination health outcomes (adjusted OR 2.41; 95 % CI: 1.05, 5.53). However, the elderly group (age > 60) showed the slow declining eGFR, it could not control diabetes compared with adult group (**Table 2**).

Table 2 The multinomial logistic regression analysis to test the association of patient-level and health service level-factors on combination health outcomes (CKD, n = 397).

Variables	Group B (Uncontrolled DM, slow CKD progression)			Group C (Controlled DM, rapid CKD progression)			Group D (Controlled DM, slow CKD progression)		
	OR	**95 % CI**	***p*-value**	**OR**	**95 % CI**	***p*-value**	**OR**	**95 % CI**	***p*-value**
Age (ref. ≤ 60)									
Age > 60	2.01	1.13 - 3.58	0.017*	1.01	0.59 - 2.03	0.988	1.86	0.94 - 3.70	0.075
BMI (ref. = normal)									
Underweight	0.89	0.21 - 3.84	0.883	0.47	0.05 - 4.53	0.516	0.32	0.03 - 3.08	0.327
Overweight	1.30	0.73 - 2.30	0.372	0.74	0.33 - 1.65	0.461	1.29	0.63 - 2.30	0.589
Obese	0.92	0.48 - 1.78	0.810	1.01	0.45 - 2.27	0.978	0.52	0.23 - 1.20	0.126
Comorbidity (ref. = mild)									
Moderate to high	1.66	0.48 - 5.71	0.424	2.39	0.56 - 10.18	0.237	1.19	0.25 - 5.57	0.825
Selfcare activities (ref. = low)									
Moderate	0.90	0.49 - 1.67	0.740	3.48	1.13 - 10.73	0.030*	1.97	0.85 - 4.62	0.116
High	1.12	0.46 - 2.74	0.800	1.42	0.27 - 7.41	0.677	3.47	1.19 - 10.15	0.023*
Integrated care (ref. = low)									
Moderate	0.62	0.22 - 1.77	0.124	0.94	0.22 - 4.05	0.932	0.81	0.24 - 2.71	0.738
High	1.18	0.61 - 2.27	0.986	1.71	0.74 - 3.99	0.211	1.12	0.53 - 2.40	0.762
Model of Care (ref. = GP + RN)									
GP + NCM	1.62	0.65 - 4.02	0.296	1.59	0.48 - 4.63	0.484	1.19	0.40 - 3.48	0.755
Specialist + NCM	1.77	0.67 - 4.69	0.248	1.36	0.36 - 5.22	0.652	0.76	0.25 - 2.29	0.625
RDU (ref. = non)									
Yes	1.59	0.75 - 3.39	0.225	1.19	0.41 - 3.42	0.752	2.41	1.05 - 5.33	0.038*
Crowding (ref. = non)									
Crowded clinic	1.77	0.67 - 4.64	0.249	1.12	0.33 - 3.86	0.856	1.51	0.47 - 4.89	0.491

Note: *Level of significant at $p < 0.05$
Reference of MLR test = Group A: Uncontrolled DM and rapid declining eGFR

Regarding with the multi-level MLR analysis, we consider the four models as presented in **Table 3**. Notice that the M1 model was nested under the M2 model which in essence was nested under the M3 model, and again this was nested under the M4 model. The results found that the M3 model was better than M1 and M 2 model with statistical significance ($p = 0.006$). The M3 model included DSCA which was a significant variable from patient-level factors. It was added the covariates from patient-level and health service-level factors included BMI, model of care and rational drug uses. The M4 model included more variables but affected the reduction of the -2LL value. Finally, the M3 model was the best fit model because of the highest significant difference in LR test. The significant association of the high-level of DSCA, model of care and rational drug uses on glycemic control and CKD progression were revealed in this model. One unit increased of DSCA and rational drug uses increased the probability of 5.36 and 2.33 times of good combination health outcomes compared with the low-level of DSCA and non-RDU group. The patients who were provided care by specialist and NCM care associated with the negative effect on combination health outcomes (odd ratio 0.40, $p = 0.004$) (**Table 3**).

Table 3 The Multi-level multinomial logistic regression model for predicting combination health outcomes of glycemic control and chronic kidney disease progression (n = 397).

Odd ratio (*p*-value)	Model 1 (n = 397)	Model 2 (n = 397)	Model 3 (n = 397)	Model 4 (n = 397)
Fixed effects				
Intercept (Uncontrolled DM and rapid declining eGFR; A)	4.31 (0.000)**	3.90 (0.000)**	3.82 (0.000)**	3.48 (0.016)*
Intercept (Uncontrolled DM and slow declining eGFR; B)	1.51 (0.121)	1.45 (0.199)	1.22 (0.514)	0.83 (0.704)
Intercept (Controlled DM and rapid declining eGFR; C)	0.23 (0.000)**	0.26 (0.000)**	0.26 (0.000)**	0.29 (0.016)*
Level 1 (Patient-level)				
DSCA (ref. = mild)				
Moderate	1.67 (0.190)	1.76 (0.148)	1.79 (0.138)	1.82 (0.128)
High	3.43 (0.016)*	3.48 (0.015)*	5.36 (0.001)**	5.80 (0.001)**
BMI (ref. = normal)				
Overweight		1.09 (0.749)	1.14 (0.657)	1.15 (0.624)
Obese		0.51 (0.076)	0.55 (0.122)	0.55 (0.126)
Underweight		0.39 (0.379)	0.42 (0.435)	0.39 (0.400)
Level 2 (Health service-level)				
Model of care (ref. = GP + RN)				
GP + NCM			0.82 (0.609)	0.90 (0.815)
Specialist + NCM			0.40 (0.004)**	0.40 (0.062)
Rational drug use (ref. = none)			2.33 (0.008)*	2.08 (0.049)*
Perceived integrated (ref. low)				
Moderate				0.97 (0.953)
High				0.73 (0.379)
Crowded (ref. = none)				1.12 (0.822)
AIC (Akaike's information criterion)	400.63	401.17	393.24	398.32
BIC (Bayesian's information criterion)	416.56	429.06	429.10	446.13
-2LL (*p*-value)	–196.31 (0.052)	–193.58 (0.061)	–187.62 (0.006)*	–187.16 (0.02)
LR-test (*p*-value)	6.35 (0.042)*	5.46 (0.141)	11.93 (0.003)*	0.92 (0.82)

Note: *Level of significant at $p < 0.05$ and **Level of significant at $p < 0.005$

Discussion

Focusing on the patient-level factors, findings revealed that the elderly participants had higher ability to control CKD progression that was congruent with the previous studies [5,33]. The anatomical changes of nephrosclerosis, globally sclerotic glomeruli and nephron hypertrophy with small cortical volume related with creatinine clearance and affected eGFR calculation [34]. Furthermore, age-related with slow declining eGFR and non-proteinuria associated with low protein intake in elderly [33], thus it might be missed diagnosis of declining eGFR in this group. Our results could not explain the association between BMI and CKD progression. Contrasted with Yun *et al.* study [35] that showed the higher incidence of CKD progression among obesity and metabolic abnormality. It could be explained by the differences of proportion of the sex, age and abnormal BMI. Almost 60 % of our participants were overweight and obese, unlikely Yun study was only 40 %. Moreover, 40 % of participants in the previous study were female differed from our study at 70 %. Female significantly associated with poor glycemic control [36] and presented with CKD more than male regarding with the association of sex hormone and insulin resistant [37]. However, this study was unable to disclose the significant difference of BMI categories.

Interesting with the major predictor of patient-level factors, the high-level of DSCA showed the significant association with combination health outcomes. Whereas the moderate level achieved only glycemic control. Findings were consistent with the previous studies of Dong *et al.* [38] that reported the increase self-care activities and glycemic control after program of health education via WeChat platform. However, lack of studies had revealed about the benefit of DSCA among diabetes with CKD patients in multi-level analysis. Generally, the recommended diet for diabetic patients were low glycemic index food with high intake of fiber and vegetable. On the other hand, CKD patients should avoid high phosphate and fiber. The relevance of DM and CKD involved in avoiding high glycemic index and fat diet. Unfortunately, analyzed by gender in this study, female reported higher levels of high glycemic index diet and did not follow healthy eating plan. The physical activity promoted the cardiometabolic function for DM and CKD patients. It could reduce muscle loss and prevent uremia in CKD patients [39]. However, most of

participants reported that they had specific exercise less than 2 days of the last 7 days. The group of poor clinical outcomes of glycemic control and CKD progression declared only 1.58 days. Prior study confirmed that poor medication adherence associated with existing proteinuria leading to rapid declining eGFR [40]. Moreover, female also missed diabetes medication recommendation more than men. However, the reporting of high level-diabetes medical adherence in our participants may influence by social desirability.

In addition, the multi-level MLR analysis found the negative association between model of care that provided by specialist and nurse case manager in tertiary care (adjusted OR 0.40; 95 % CI: 0.21, 0.4) on combination health outcomes. In the midst of health care delivery system in Thailand, the tertiary care with specialist model account for complex diseases more than the primary care. This study is consistent with previous study of the older diabetic patients in tertiary care revealed that two thirds of them had tight glycemic control by oral hypoglycemic agents and insulin plus. More than half of them presented with CKD and one fourth had diabetic retinopathy. This indicated that the specialist clinic in tertiary care dominated patient with more comorbidities. However, the clinical health outcomes were not significant [41]. Primary and secondary care mostly use GP and RN or GP and NCM model of care. Registered nurses and nurse case manager in diabetic clinic were trained and responsible for foot or eye examination. A trained nurse uses telemedicine as a tool for interpretation and consultation with specialist under the limited resource of Thailand. The variation of health outcomes in hospital level demonstrated the effectiveness and limitation of model of care in the situation of outpatient utilization in district level. The district level hospital strongly associated with higher hospital ratio for uncontrolled diabetes and chronic complication [42]. The outpatient utilization concentration was positively correlated with ambulatory specific condition of diabetes. Patient perception corresponded to provider type and could predict satisfaction [43]. For this reason, the real situation of hospital level requires a tailor-made structure based on resource availability.

This study also demonstrates the benefit of rational drug uses (RDU) prescription on combination health outcomes tested by MLR analysis. Considering with KDIGO guideline, metformin prescription was recommended to continue use in patient with eGFR > 60 mL/min/1.73 m^2 and review prescription in those with eGFR 30 - 44 mL/min/1.73 m^2 and discontinued in eGFR less than 30 mL/min/1.73 m^2. The initiation of insulin or other non-nephrotoxic drug such as sodium glucose transporter (SGLT-2) inhibitors or DPP-4 inhibitors should be considered by physician when the eGFR less than 30 mL/min/1.73 m^2. The percent concordance with guideline of metformin was 73.05 % in this study. It could not achieve the key performance indicator of Ministry of Public Health (MOPH) in Thailand at 80 % but higher than other developed country [21,44]. The prescribing rate may affect by the health care coverage scheme. Seventy-two percent of the population were covered by the Universal Coverage Scheme, 17 % by government welfare and another by the Social Security scheme. The Comptroller General's department (CGD) accounted for medication disbursement aligned with the Thailand nationalist of essential medicines (NLEM). MOPH policy makers implemented the rational drug uses prescription policy. However, Thailand service plan recommended the metformin prescription for diabetic patient who had eGFR more than 30 mL/min/1.73 m^2. It differed from KDIGO guideline that advised to adjusted dose when eGFR 30 - 44 mL/min/1.73 m^2. Physicians were encouraged the rational uses of medicine by adopt key performance indicator of service plan. Prescribing RDU were more efficient, expedient and affordable by CGD. However, the physician had chance to prescribe the appropriate medicine with their judgement based on individual patient needs. Therefore, the minority of patients who had specific limitation or complication were prescribed with second line drug of NLEM without patient's copayment. In contrast, the study in developed countries found only the percentage of concordance with guideline was 45 - 58.3 % [21,44]. According to the study of Winocour [45], it indicated that the current guideline was inconvenient to integrate care for this high-risk group because metformin had adverse effect in renal impairment patients. Doctor might hesitate to continue metformin and prefer to use new drug regimens which are beneficial for cardiovascular risk but low risk of hypoglycemia and renal impairment. Unfortunately, this finding found that the percentage of NSAIDs prescription reached to 37.53 % which was higher than target limit 10 % of guideline recommendation. Comparison between group found that the higher percent prescription of NSAIDs group had lower percent prescription of metformin. Consistent with the trend of increase percentage of NSAIDs uses in US [46]. This irrational drug uses leaded to poor glycemic control with rapid CKD progression and eventually to ESRD [47]. Indeed, NSAIDs prescription should be avoided and restricted in CKD patients.

According to the core component of integrated care, almost half of participants perceived the low-level of care coordination. Five hospitals in this study, primary care setting, provided care by GP and RN. The services tended to be less complexities than tertiary care provided by specialist. The participants reported the lack coordination and continuing care such as home visit, phone consultation and referral communication. Previously, Zimbudzi [48] showed the effective of integrated care service which provided

phone advice. This integrated care focused on coordinated care and seamless with appropriate management contributed to quality of care, accessibility to interdisciplinary team, and continuing care by follow-up via telephone aided. It implied that the conventional care delivery did not meet the patient needs. Some countries, nurse practitioners (NP) in community-based clinic provided more coordination and self-management support for chronic disease [49,50]. The benefit of community-referral and continuity care not only mitigate crowding but also increase available service time. Task allocation between NPs and GPs contributed to helpful and collaborated practice especially for complex diseases in primary care. NPs should upskill the clinical competencies and knowledge to accomplish the optimal goals. The job description and regulation should be clarified role and responsibility. However, nurse roles varied depending on complexity, practice and the legal restriction of practice [50].

Mostly, nine of eleven settings faced with crowded clinic which had service time less than 10 min as WHO recommendation. Although there was not significant difference in glycemic control and CKD progression, the patients who had low to moderate level of self-care activities associated with negative outcomes in crowed clinic. The previous study in Thailand revealed that the average number of physicians and nurse per 10,000 population were only 3.9 and 27.3 in 2015, respectively. The proportion of physicians had significant negative association with uncontrolled DM and chronic complication rate [40]. The shortage of physician and nurse who provided care affected the consultation or service available time. They had no adequate time to investigate, inquire and advise the specific self-care activities. This unavailable service time may influence the clinical outcomes. Similar with Vare's study that revealed the specialty clinic had optimal time for comprehensive patient assessment, self-management support, bridging communication and treatment [51].

Conclusions

These findings imply the strong predictors consisting of diabetes self-care activities and rational drug uses prescription which increase probability to achieve glycemic control and slow CKD progression. Surrounding with crowded clinic, the negative outcomes should be aware in low-level of self-care activity, obese and younger age. The high level of integrated care for this high-risk group, particularly in the crowded clinic should be performed. This study encourages professional nurses and health care providers to promote the model of care that appropriate for individual person who had the difference of age, BMI and self-care activities level. In health service-level, the rational drug uses prescription and integrated care for diabetic patient with CKD should be concerned. Suggesting the certified and up-skill training program to optimize service accessibility based on integrated care and health resource availability.

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