

Health Data Science

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[AP3-E2-3-02] Effects of Renal Dysfunction on the Improvement of Anemia in Bangladesh: An Epidemiological Analysis of Health Checkup Data with ICT Intervention

*Mariko Nishikitani^{1,2}, Yasunobu Nohara³, Rafiqul Islam Maruf¹, Fumihiko Yokota², Kimiyo Kikuchi⁴, Ashir Ahmed^{2,5}, Nazneen Sultana⁶, Naoki Nakashima^{1,2} (1. Medical Information Center, Kyushu University Hospital, Japan, 2. Institute of Decision Sciences for a Sustainable Society, Kyushu University, Japan, 3. Faculty of Advanced Science and Technology, Kumamoto University, Japan, 4. Department of Health Sciences, Faculty of Medical Sciences, Kyushu University, Japan, 5. Graduate School of Information Science and Electrical Engineering, Kyushu University, Japan, 6. Grameen Communications, Bangladesh)

Keywords: Hemoglobin, Urine Protein, Health Checkup, Bangladesh, Multilevel Model

The association between improvements in anemia in regions with high urine protein (UP) was examined epidemiologically using the results of regional health checkups. The study hypothesis was that mild renal dysfunction emerging along with abnormal UP hindered improvements in hemoglobin (Hb) despite health checkups.

Of 14,906 first-time subjects who received a remote health checkup between 2012 and 2014, data from 3,104 subjects who had their Hb tested were collected from 13 regional sites for analysis. The average Hb was 11.5 (SD1.4) g/dl, indicating 1,821 (59%) had anemia, and 916 (30%) had abnormal UP. A statistically significant association between UP and anemia ($p = 0.002$) was shown. Considering this first checkup as an intervention, 350 women received checkups again after 2–4 months. The women were divided into two groups based on having abnormal UP or not and were compared.

No statistically significant difference was found between the two groups at baseline in terms of Hb, anemia, iron prescription rate, or age. At the second checkup, Hb significantly increased in each group. The positive increase in Hb in this period in the two groups were 0.5 (SD1.5) g/dl and 0.7 (SD1.5) g/dl, respectively, and the difference was statistically significant ($p = 0.0291$). In the multilevel analysis considering the time and the various survey sites, prescribed iron was shown to contribute to Hb improvements (Coefficient 0.65, $p < 0.001$). The presence of UP also tended to impair Hb improvements, but the difference was not significant (Coefficient -0.24, $p = 0.085$).

In this study, the health checkup interventions improved Hb levels and decreased the prevalence of anemia, mainly due to iron supplements. Regarding the negative effect of UP on the improvement of Hb, there was some evidence that Hb improvements were impaired among subjects suspected of having mild renal dysfunction.

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Mariko Nishikitani^{a, b}, Yasunobu Nohara^c, Rafiqul Islam Maruf^a, Fumihiko Yokota^b, Kimiyo Kikuchi^d, Ashir Ahmed^{b, e}, Nazneen Sultana^f and Naoki Nakashima^{a, b}

^a Medical Information Center, Kyushu University Hospital, Japan

^b Institute of Decision Sciences for a Sustainable Society, Kyushu University, Japan

^c Faculty of Advanced Science and Technology, Kumamoto University, Japan

^d Department of Health Sciences, Faculty of Medical Sciences, Kyushu University, Japan

^e Graduate School of Information Science and Electrical Engineering, Kyushu University, Japan

^f Grameen Communications, Bangladesh

Abstract

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Of 14,906 first-time subjects who received a remote health checkup between 2012 and 2014, data from 3,104 subjects who had their Hb tested were collected from 13 regional sites for analysis. The average Hb was 11.5 (SD1.4) g/dl, indicating 1,821 (59%) had anemia, and 916 (30%) had abnormal UP. A statistically significant association between UP and anemia ($p = 0.002$) was shown. Considering this first checkup as an intervention, 350 women received checkups again after 2–4 months. The women were divided into two groups based on having abnormal UP or not and were compared.

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In this study, the health checkup interventions improved Hb levels and decreased the prevalence of anemia, mainly due to iron supplements. Regarding the negative effect of UP on the improvement of Hb, there was some evidence that Hb improvements were impaired among subjects suspected of having mild renal dysfunction. This study also indicated the usability of an extensive collection and practical analysis of patient data that can be obtained by e-health checkups and telemedicine consultations.

Keywords:

Hemoglobin, Urine Protein, Health Checkup, Bangladesh, Multilevel Model

Introduction

Bangladesh is a developing country, and people are suffering from lifestyle diseases. In 2016, the cause of death due to lifestyle diseases was 67 percent [1]. There is an under-developed social infrastructure of public health insurance and a shortage of health care facilities. However, there is an information and communication technology (ICT) system for mobile phones and a pharmacy in almost every rural area and village.

To assess the effect of an e-health examination on lifestyle diseases, our team conducted a preventive program using medical sensor packages and remote medical examinations by using the ICT system from 2012–2014 [2]. Physical measurements and biological and biochemical data were assessed, and about one-third of the participants were determined to have some degree of lifestyle related diseases such as high blood pressure, overweight, and/or diabetes [3]. Interestingly, urine protein (UP) tests showed a relatively high prevalence, and some survey regions had a higher prevalence than others.

As another health indicator, the high prevalence of low hemoglobin (Hb) and anemia has raised concern in the context of maternal and child health. In Bangladesh, more than half of adolescent girls (10–19 years old) have been reported to have anemia (51.6%, $n = 1,314$) with less than 12g/dl Hb [4], and 42% of women of childbearing age have anemia [5]. Previous studies have found that iron deficiency is a major cause of anemia in developing countries [6], and it has also been shown that interventions by repeated health examinations and subsequent health education can improve Hb levels [7].

The high prevalence of UP was concentrated in some survey areas, such as northwestern areas and at the mouth of the Ganges River of Bangladesh [3]. The cause of the abnormal levels of UP has been known as the first stage of various health problems, such as fatigue, urine infections, renal dysfunction, and life-related diseases, hypertension, diabetes, and cancer. In some cases which observed at a particular group, such as occupation and resident, the mild renal dysfunction could be caused by some environmental exposure. In the case of renal dysfunction due to environmental and occupational exposure, such as heavy metals, organic solvents, and pesticides, high

urinary protein occur as a subclinical manifestation of initial renal dysfunction [8].

The relationship between proteinuria and Hb is not still well understood, but once renal dysfunction develops into chronic kidney disease (CKD), it is thought to contribute to anemia. Although the cause of anemia varies, erythropoietin (EPO), which is necessary for the process of erythrocyte differentiation and maturation, is produced in the interstitium near the proximal tubule of the kidneys [9]. Thus, if patients with CKD develop anemia, recovery of their Hb levels might difficult [10]. However, EPO levels in CKD patients are not always low [11]. In addition, iron metabolism is strongly connected to anemia, and the involvement of the hepcidin peptide (HP), which works as a suppresser of iron absorption in the body, has been highlighted. However, HP concentrations are high in CKD patients due to various possible mechanisms [11]. Given multiple complicated mechanisms are involved, the relationship between mild impairment of renal function and the inhibition of Hb levels is not well understood.

In this study, given the urinary protein abnormality observed in Bangladesh (slight renal dysfunction), the association between improvement of anemia was examined epidemiologically using the results of regional and occupational health checkups. The prevalence of abnormal UP was 35% of the total at the previous analysis, and the high incidence of UP were concentrated in some survey areas [3]. Therefore, abnormal UP observed in this survey might derive from mild and chronic renal dysfunction might, and it might induce some physiological problems relating to metabolic imbalance and the cause and recovery from anemia. The study hypothesis was that the interventions by prescription of iron tablets and lifestyle instructions might not improve Hb levels sufficiently in those subjects with mild renal dysfunction.

Materials and Methods

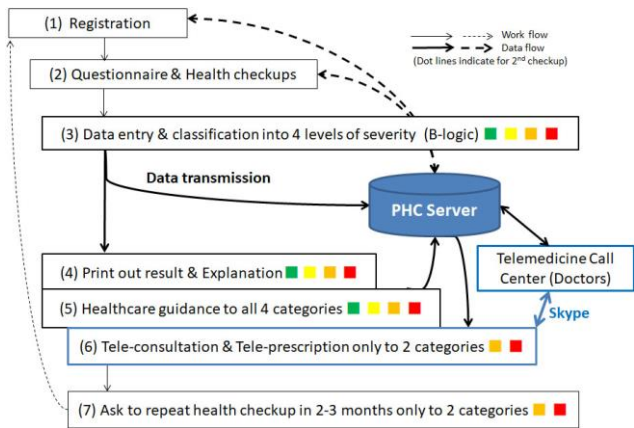


Figure 1- Work flow and data flow chart of the health checkups and telemedicine.

Subjects

From 2012 to 2014, medical devices equipped with a communication function "BAN" and a tablet PC were packaged and delivered to the workplace or a non-medical village for health checkups and telemedicine (Figure 1). The measurement data were classified into 4 levels according to severity, based on international diagnostic criteria (Table 1). For those who were judged to have the more severe levels of "affected" or "emergent (treatment)," ICT intervention was conducted; the doctor at the call center provided telemedicine using Skype and gave

instructions such as a prescription, lifestyle instructions, and referrals to hospitals. If subjects had any abnormal test value at the initial health checkup, in addition to providing these instructions, they were offered another health checkup again after 2 to 3 months to assess any improvement. More detailed information has been reported previously [2], [3], [7].

Table 1. Bangladesh-logic (B-logic) criteria for risk stratification

	Normal	Caution(subnormal)	Affected (Remote medicine)	Emergent (Remote medicine + Encouragement to visit clinic)
Waist	Male <90cm Female <80cm	90cm ≤ 80cm ≤		
Waist/Hip Ratio	Male <0.90 Female <0.85	0.90 ≤ 0.85 ≤		
Body Mass Index	<25	25 ≤, <30	30 ≤, <35	35 ≤
Blood Pressure	<130 mmHg <85 mmHg	130 ≤, <140 mmHg 85 ≤, <90 mmHg	140 ≤, <180 90 ≤, <110	180 ≤ 110 ≤
Fasting Blood Sugar	<100mg/dl	100 ≤, <126mg/dl	126 ≤, <200mg/dl	200mg/dl ≤
Postprandial Blood Sugar	<140mg/dl	140 ≤, <200mg/dl	200 ≤, <300mg/dl	300mg/dl ≤
Urine Protein	-	±	+	±
Urine Sugar	-	±	+	±
Urobilinogen	±	±	+	±
Pulse Ratio	60 ≤, <100	50 ≤, <60 100 ≤, <120	<50 120 ≤	
Arrhythmia	None		+	
Smoking	None	+		
Body Temperature	<37℃	37℃ ≤, <37.5℃	37.5℃ ≤	
SpO ₂	≥ 96%	93 ≤, <96	90 ≤, <93	<90%
Hemoglobin	≥ 12g/dl	10 ≤, <12g/dl	8 ≤, <10g/dl	<8g/dl

In this study, out of 14,906 first-time subjects who received the first health checkup during the study period, data from 350 women were analyzed because all data on Hb and UP levels from both health checkups were available.

Ethical Considerations

The Kyushu University Institutional Review Board for Clinical Trials approved the protocol of this verification study in 2012 (Approved Number: 24-048), and 2018 (Approved Number: 20182007).

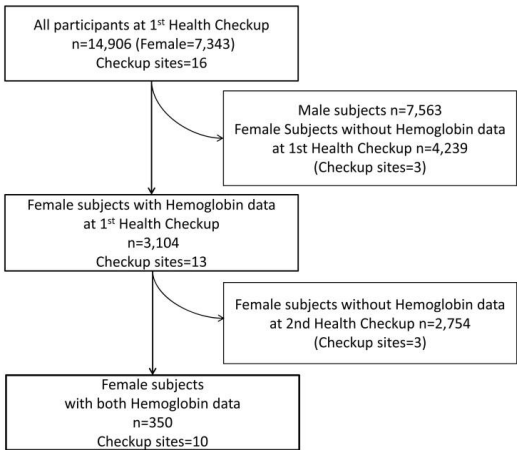


Figure 2- Process of selection of study subjects.

Statistical Analysis

Study subjects were divided into two groups: subjects with abnormal UP levels and subjects without abnormal values of UP. Then, Hb levels at the first baseline checkup and that of the second checkup were simply compared. At the first checkup, some subjects received iron tablets. The ages were from 18 to 65, and both age and the use of iron tablets could affect Hb values, so a regression analysis was conducted next. The degree of improvement in the Hb levels of both groups after the two health checkups was evaluated by regression analysis using a mixed-effects multilevel model nested in individuals (lower level) and survey sites (upper level) [12]. In the multi-level analysis, an interaction term based on the variables

siteLocation	siteType ^a	n	Age	Hb mean	Hb range	Anemia+	UP(+)	2nd ^b
Dhaka	U	18	28.2 (2.9)	12.2 (0.9)	10.1-13.5	7 (39%)	2 (11%)	3
Dhaka	U	489	26.0 (3.7)	11.6 (1.3)	5.2-14.9	262 (54%)	58 (12%)	75
Shariatpur	R	326	29.6 (5.4)	11.5 (1.5)	4.5-14.3	188 (58%)	58 (18%)	32
Gazipur	SU	79	26.5 (3.1)	12.0 (1.3)	7.0-14.8	35 (44%)	15 (19%)	0
Gazipur	SU	128	27.0 (3.5)	12.0 (1.2)	8.6-14.6	67 (52%)	24 (19%)	0
Gazipur	SU	600	27.1 (3.2)	12.0 (1.3)	6.2-15.9	294 (49%)	127 (21%)	0
Dhaka	U	94	27.5 (3.9)	11.4 (1.2)	8.7-14.2	62 (66%)	27 (29%)	22
Chittagong	R	255	30.8 (4.7)	11.9 (1.4)	7.2-15.6	126 (49%)	78 (31%)	42
Dhaka	U	65	26.8 (3.7)	11.9 (1.5)	6.0-15.0	31 (48%)	23 (35%)	18
Chittagong	R	191	32.6 (6.0)	11.9 (1.3)	7.5-14.5	87 (46%)	71 (37%)	16
Dhaka	U	66	37.8 (7.8)	11.3 (1.4)	7.9-14.9	45 (68%)	25 (38%)	11
Rajshahi	R	501	33.9 (7.9)	10.9 (1.4)	5.4-14.3	387 (77%)	233 (47%)	79
Thakurgaon	R	292	33.4 (8.6)	10.6 (1.6)	4.8-14.7	230 (79%)	176 (60%)	52

^a U: urban area, R: rural area, and SU: suburban area.

^b The column of "2nd" indicates the subjects number who received health checkups again after the first one.

representing first and second the health checkups and the urinary protein abnormality level was added, and the degree of Hb change in the two groups, with and without abnormal urinary protein, was compared. All statistical tests were performed using STATA 16.0, and the statistical significance level was set 5%.

Results

Of the 14,906 study participants who received the mobile health checkup at the first survey, 3,104 female subjects had their Hb levels measured. Figure 2 shows the protocol for inclusion and exclusion for the 350 women who received Hb testing at both the first and second health checkups.

Table 2 shows the basic characteristics by surveyed regions of the 3,104 subjects whose Hb was measured at the first medical examination. There were 5 urban areas, 3 suburban areas, and 5 rural areas, and 5 urban areas (Dhaka) and 3 suburban areas (Gazipur) included workers groups. The average age of the females who had their Hb levels measured was 29.7 (SD6.4) years, with an average Hb level of 11.5 (SD1.4) g/dl, and 1,821 (59%) had anemia. The number of subjects with urinary protein was 916 (30%). There was a significant association between high urinary protein levels and anemia ($p = 0.002$). Of the 13 health check-up areas, 3 Gazipur regions were not available for a second health check-up, so the data was ultimately obtained from the 10 remaining sites (Figure 2).

Table 3. Hemoglobin (Hb) and anemia of the two groups with (+) and without (-) urine protein (UP) in health checkups

	Total (n=350)	UP+ (n=161)	UP- (n=189)	p ^b
UP ^a (-)	189 (54%)	0 (0%)	189 (100%)	
(±)	62 (18%)	62 (39%)	0 (0%)	
(+)	78 (22%)	78 (48%)	0 (0%)	
(++)	8 (5%)	8 (11%)	0 (0%)	
(+++)	3 (1%)	3 (2%)	0 (0%)	
Age	31.7 (6.8)	31.7 (6.4)	31.7 (7.1)	0.9087
Iron tablets	131 (37%)	56 (35%)	75 (40%)	0.345
Hb1 (1st)	10.9 (1.7)	11.0 (1.6)	10.7 (1.8)	0.1306
Hb1 range	4.8-15.1	4.8-15.01	6-14.4	
Anemia1	246 (70%)	118 (73%)	128 (68%)	0.256
Hb2 (2nd)	11.5 (1.3)	11.5 (1.2)	11.5 (1.4)	0.4754
Hb2 range	5.3-14.3	5.3-14.2	6.1-14.3	
Anemia2	206 (59%)	98 (61%)	108 (57%)	0.480
Difference of Hb	0.6 (1.5)	0.5 (1.5)	0.7 (1.5)	0.0291
p ^c (1st vs 2nd)	<0.0001	0.0013	<0.0001	

^a The semi-quantitative analysis by the dipstick method decided the level of UP.

^b Wilcoxon rank sum test for continuous data, and χ^2 test for categorical data.

^c Wilcoxon signed rank test.

The study subjects, 350 females who received two medical examinations, were divided into two groups according to the presence or absence of urinary protein. Their Hb levels and anemia status are shown in Table 3 together with the results of UP levels, their age, and the status of iron prescription at the baseline medical checkup. The box plots are shown in Figure 3 for the changes in Hb levels and the results of simple comparisons of the two health checkups and between the groups. There was no significant difference between the two groups at baseline (1st checkup) in Hb levels, the prevalence of anemia, iron prescription rates, or age (Table 3). There was also no difference between these groups in these values at the second health checkup a few months after the first health checkup. However, within each group, the intervention Hb levels were significantly increased (UP(+) group $p = 0.0013$, UP(-) group $p < 0.0001$, by Wilcoxon signed-rank test), and the prevalence of anemia was slightly decreased. (UP(+) group $p = 0.0047$, UP(-) group $p < 0.0039$, by McNemar test). The Hb levels changed significantly in the UP+ and UP- groups by 0.5(SD1.5)g/dl and 0.7(SD1.5)g/dl, respectively ($p = 0.0291$).

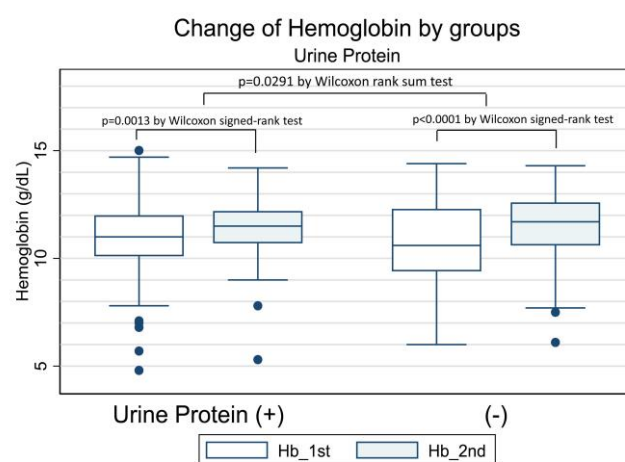


Figure 3- Change in hemoglobin (Hb) between the 1st and 2nd health checkups by groups of with (+) and without (-) urine protein

Table 4 shows the results of the regression analysis using 3 multilevel models to confirm the effect of improving Hb levels on those subjects with and without abnormal urinary protein. The changes in Hb levels by the 1st health checkup intervention were indicated by the interaction term with the "time" (1st

Table 4. Estimation result of Mixed-effects Multilevel Regression (Correlation Coefficient: Coef.)

	Model A			Model B			Model C		
	Coef.	SE	95%CI	Coef.	SE	95%CI	Coef.	SE	95%CI
[Fixed effects]									
Intercept	11.15	0.393	10.38, 11.92	10.67	0.386	9.909, 11.42	11.06	0.396	10.29, 11.84
Age	-0.012	0.010	-0.033, 0.008	-0.013	0.010	-0.033, 0.008	-0.013	0.010	-0.033, 0.008
Time	0.471	0.104	0.267, 0.674	0.796	0.095	0.610, 0.982	0.541	0.111	0.322, 0.759
Iron tablet	-1.891	0.275	-2.430, -1.352	-0.906	0.139	-1.178, -0.635	-1.884	0.274	-2.421, -1.346
Iron tablet x Time	0.651	0.158	0.342, 0.961	-	-	-	0.650	0.158	0.341, 0.959
UP	-	-	-	-0.239	0.141	-0.515, 0.037	-0.235	0.138	-0.505, 0.036
UP x Time	0.185	0.063	0.062, 0.307	0.490	0.180	0.137, 0.842	0.465	0.177	0.119, 0.811
[Random effects]									
Site (intercept)	0.055	0.049	0.010, 0.310	0.057	0.049	0.010, 0.310	0.054	0.048	0.010, 0.305
Individual (intercep	1.006	0.122	0.793, 1.277	0.980	0.123	0.767, 1.252	1.006	0.122	0.793, 1.276
Residual	1.018	0.077	0.878, 1.181	1.062	0.080	0.915, 1.231	1.012	0.077	0.873, 1.174

= 0 and 2nd = 1) of checkups by the prescription of iron (not prescribed = 0 and prescribed = 1; Model A) or/and UP ("-" = 0 and "+" = 1; Model B). As the coefficient of the "time" indicated a significant positive value, the intervention of the first checkup significantly improved the Hb value. Similarly, the interaction term with "time" indicated significantly positive, prescribed iron showed to contribute to the improvement (Coefficient 0.65, $p < 0.001$ in Model B and Model C) (Table 4). We also found that the abnormal levels of urinary protein also had a tendency to impair the improvement in Hb levels, but the difference was not significant (Coefficient -0.24, $p = 0.085$ in Model B and Model C) (Table 4).

Discussion

In this study, we found that health checkup intervention improved Hb levels and decreased the prevalence of anemia. It was also shown that iron tablets worked effectively to improve Hb levels. As this study confirms, the prevalence of anemia among women of reproductive age in developing countries is generally high [13]. From the significant improvement due to the use of iron supplements, continuum intervention via health checkups together with lifestyle and health education, including diet and nutritional information, appear to be useful.

As the main hypothesis of this study, we examined the possibility that urinary protein levels would impair the recovery of Hb levels in subjects suspected of having renal dysfunction. The hypothesis was nearly confirmed, but ultimately was not. In the simple comparison, the changes in Hb levels in the group with abnormal levels of UP were significantly smaller than those in the group with normal UP levels, and it was difficult to improve Hb levels in those with abnormal UP. On the other hand, according to the results of the multilevel analysis adjusted for age and regional information, the use of iron tablets led to a smaller change in Hb levels in the group with abnormal urinary protein levels but statistically, the difference was not significant.

The cross-sectional analysis of the prevalence of anemia and urinary protein showed a statistically significant association. Those with low Hb values were at risk of having abnormal UP. However, the fact that the statistical results did not match the study subjects who were subsequently analyzed might be related to a selection bias among the subjects. In some regional areas, the second health checkup could not be performed, and those who received the second medical examination had other abnormalities such as hypertension, obesity, urinary glucose, and other factors, in addition to the results for urinary protein

and anemia, because they had been encouraged to receive a second health checkup again for these conditions. Therefore, the selected study subjects had problems in addition to anemia and renal dysfunction and these conditions might have affected the results. In addition, there had been the interesting on the context of maternal and child health, and this study subjects were women and sampled subjects who receiving Hb test was biased toward younger subjects (median: 31.7, 25%-75%: 26-35 years). The results might have been different with the participation of more male subjects and older adults.

The dataset collected by e-health checkups and telemedicine consultations could be subjected to a complete statistical analysis, which could sometimes reveal hidden co-relations between certain parameters which were never looked into, like anemia and renal dysfunction in this study. Such extensive e-health intervention can give us new insights into relationships between physical, biological, and biochemical parameters, which can help in detecting early deviation from health, initial management, and better prognosis.

Limitations

There are several limitations in this study. First, regarding anemia and renal dysfunction, the data collected at the health checkups of residents and at workplaces, and a definitive diagnosis and decision of causality, have not been conducted. For example, in the case of anemia, Hb is a powerful diagnostic criterion, and WBC (white blood cell) and other blood components, MCV (mean corpuscular volume), and EPO should have been measured to determine the cause of the anemia [14]. In addition, UP is not a definitive test for renal dysfunction and the possibility of false-positive should be considered. In this study, the number of subjects with abnormal UP was much higher than in developed countries [3], and slight and chronic renal dysfunction was suspected due to exposure to regional and living environmental factors. Typically, these factors are combined with investigations of laboratory tests such as urine sedimentation and other blood biochemical tests to assess general morbidity, including renal function [8]. The main objective of this study was the survey by screening, and these laboratory investigations were not conducted. Conducting such tests would be important in a future study and it would enable us to assess the effect of false-positive and specificity. In addition, , which used the general-purpose tablets, such as, FEROCIT, FEOFOL-CI, and IPEC-PLUS etc. we have no information on the iron tablets prescription regarding whether or not subjects actually took the medication. However, there was no difference in prescription rates and no difference in the proportion of subjects with anemia, so it is not expected that only one

group would have higher compliance. Therefore, the lack of information on this point should have little effect on the results of this study.

Conclusion

This study showed that the administration of iron supplements was significantly effective in improving anemia in Bangladesh. Regarding the relationship between renal dysfunction and improvement of anemia, there was some evidence that Hb levels did not improve sufficiently in subjects suspected of having mild renal dysfunction. Paradoxically, in the absence of intervention, anemia might not improve or might need more time to improve in areas with many residents with mild renal impairment. Therefore, it is possible that slight renal dysfunction is one of the factors behind the high prevalence of anemia in Bangladeshi women. To determine causal relationship between renal dysfunction and anemia, future studies are warranted that have more general participant inclusion and with a more detailed analysis of the diagnosis of renal dysfunction. Moreover, this study indicated the usability of an extensive collection of patient data that can be obtained by e-health checkups and telemedicine consultations. Practical analysis of these e-health data can enable us to help in detecting early deviation from health, initial management, and better prognosis.

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Address for correspondence

Dr. Mariko Nishikitani

Medical Information Center, Kyushu University Hospital
CollaboII-705, 3-1-1 Maidashi, Higashi-ku
Fukuoka 812-8582, Japan
E-mail: nishikitani.mariko.585@m.kyushu-u.ac.jp