



Title	Problems in methods for the detection of significant proteinuria in pregnancy
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1 **Revised***[Original Article]* for JOGR

2 **Problems in methods for the detection of significant proteinuria in pregnancy**

3

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16

17 **Running foot:** Problems in detection of proteinuria

18 **Abstract**

19 **Objective**

20 To underscore problems associated with the dipstick test and determination of protein
21 concentration alone in spot-urine (P-test) compared with spot-urine protein-to-creatinine
22 ratio (P/Cr test) and to determine whether urine collection for 24-h test was complete.

23 **Methods**

24 Dipstick and P/Cr tests were performed simultaneously in 357 random spot-urine
25 specimens from 145 pregnant women, including 35 with preeclampsia. Positive results
26 were defined as $\geq 1+$ on dipstick test, protein concentration ≥ 30 mg/dL on P-test, and
27 P/Cr ratio ≥ 0.27 (mg/mg) on P/Cr test. Sixty-four 24-h urine tests (quantification of
28 protein in urine collected during 24 h) were performed in 27 of the 145 women. We
29 assumed that P/Cr ratio ≥ 0.27 predicted significant proteinuria (urinary protein ≥ 0.3
30 g/day). The 24-h urine collection was considered incomplete when urinary creatinine
31 excretion < 11.0 mg/kg/day or > 25.0 mg/kg/day.

32 **Results**

33 Forty-four percent (69/156) of specimens with a positive test result on dipstick test
34 contained protein < 30 mg/dL. Dipstick test was positive for 25.7% (69/269) of
35 specimens with protein < 30 mg/dL and for 28.8% (79/274) of specimens with P/Cr ratio
36 < 0.27 . P-test results were positive for 7.3% (20/274) and negative for 18.1% (15/83) of
37 specimens with P/Cr ratio < 0.27 and ≥ 0.27 , respectively. Incomplete 24-h urine
38 collection occurred in 15.6% (10/64) of 24-h urine tests. Daily urinary creatinine
39 excretion was 702–1397 mg, while creatinine concentration varied from 16 mg/dL to
40 475 mg/dL in spot-urine specimens.

41 **Conclusion**

42 Dipstick test and P-test were likely to over- and underestimate risks of significant
43 proteinuria, respectively. The 24-h urine collection was often incomplete.

44 **Key Words:** proteinuria, creatinine in the urine, protein to creatinine ratio

45

46 INTRODUCTION

47 Assessment of proteinuria is an important constituent of antenatal care for pregnant
48 women. The gold standard test for determination of significant proteinuria in pregnancy
49 is currently confirmation of protein ≥ 0.3 g/day in the urine collected for 24 hours (24-h
50 urine test). The dipstick test, which can be used for semiquantitative determination of
51 protein concentration in the spot-urine, is used as a screening test for detection of
52 significant proteinuria. However, concerns have been raised regarding the accuracy of
53 dipstick testing [1 – 7]. The amount of proteinuria increases with advancing gestation
54 [8], but we frequently encounter pregnant women who exhibit a negative result after
55 showing a positive result on dipstick testing. Further problems of 24-h urine testing,
56 such as incomplete urine collection and inconvenience for both patients and obstetric
57 service providers, have also been reported [9].

58 The Australian Society for the Study of Hypertension in Pregnancy and the
59 International Society for the Study of Hypertension in Pregnancy have proposed use of
60 the urinary spot protein-to-creatinine ratio (P/Cr test) as an alternative to 24-h urine test
61 [10, 11]. A systematic review by Cote et al. [12] concluded that P/Cr test with a
62 threshold of 0.265 (mg/mg) is a reasonable “rule-out” test for detecting proteinuria ≥ 0.3
63 g/day in pregnancy. However, this issue has not been studied extensively among
64 pregnant Japanese women and P/Cr test is not widely used at present in Japan.
65 Accordingly, we conducted this retrospective study to underscore the problems in the
66 dipstick test, determination of protein concentration alone in the spot-urine (P-test), and
67 24-h urine test.

68

69 METHODS

70 This study was conducted after receiving approval from the Institutional Review Board
71 of Hokkaido University Hospital, a tertiary teaching hospital managing mainly high-risk
72 pregnant women. Beginning in 2009, we introduced determination of urinary
73 protein-to-creatinine (P/Cr) ratio (mg/mg) as a routine test for outpatients exhibiting a
74 positive result ($\geq 1+$) on dipstick test. Routine laboratory work-up included

75 determination of P/Cr ratio for inpatients with edema and/or hypertension. This method
76 was designated as P/Cr test in this study and a positive test result was defined as a P/Cr
77 ratio ≥ 0.27 (mg/mg).

78 **Of 483 women who gave birth at the Hokkaido University Hospital during the**
79 **period between January 2011 and July 2012, 145 women underwent both dipstick**
80 **and P/Cr tests simultaneously in a total of 357 random spot-urine specimens ($2.5 \pm$**
81 **1.5 times [range, 1 – 7]/person) and all of the 145 women were included in this**
82 **study.** A total of 64 \times 24-h urine tests were performed in 27 women, two of whom
83 provided aliquots of 5 mL of random spot-urine specimens three times before mixture
84 of their spot-urine with the whole urine for the 24-h urine test. These 6 spot-urine
85 specimens were used for the P/Cr test.

86 The dipstick used in the dipstick test was designed to be negative, 1+, 2+, and $\geq 3+$ on
87 visual judgment for protein concentrations in the urine of < 30 , 30 – 99, 100 – 299, and
88 ≥ 300 mg/dL, respectively, according to the manufacturer's package insert (Siemens,
89 Tokyo, Japan). The protein and creatinine concentrations in the urine were measured
90 using the pyrogallol red method (Wako, Osaka, Japan) and creatinase sarcosine oxidase
91 peroxidase method (Mitsubishi Chemical Medience, Tokyo, Japan), respectively, at our
92 institution. Data on age, body weight, parity, and clinical outcomes were obtained from
93 the medical records. The term "P-test" was used for the determination of urinary protein
94 concentration alone in spot-urine in this study.

95 All of the data are presented as the mean or median values. The unpaired t test,
96 Kruskal–Wallis test, and Mann–Whitney U tests were used to analyze the results.
97 Fisher's exact test was used for comparison of frequencies. The software package
98 StatView 5.0 for Macintosh (SAS Institute Inc. Cary, NC) was used for all the statistical
99 analyses, and $P < 0.05$ was taken to indicate significance.

100

101 RESULTS

102 *Accuracy of dipstick test and P-test for prediction of protein concentration ≥ 30 mg/dL*

103 *and/or P/Cr ratio ≥ 2.7*

104 Of the 357 spot-urine specimens, 201 showed a negative result and the remaining 156
105 showed a positive result ($\geq 1+$) on the dipstick test (Table 2). Dipstick test was positive
106 in 87 of the 88 specimens with $[P] \geq 30$ mg/dL, giving a sensitivity of 98.9% for
107 prediction of $[P] \geq 30$ mg/dL (Table 3). Sixty-nine (44%) of the 156 specimens with a
108 dipstick test result $\geq 1+$ contained protein < 30 mg/dL. Dipstick test was falsely positive
109 in 25.7% (69/269) of specimens with $[P] < 30$ mg/dL. The mean $[P]$ values were $3.9 \pm$
110 7.1 , 24.2 ± 14.9 mg/dL, 91.1 ± 55.0 mg/dL and 289.3 ± 243.9 mg/dL for negative, 1+,
111 2+, and 3+ results on dipstick test, respectively. Thus, the dipstick test used in this study
112 was designed to give a positive result in urine with a far lower $[P]$ than that described on
113 the package insert.

114 P/Cr test was positive in 83 specimens from 39 women who developed preeclampsia or
115 gestational proteinuria. The 39 women provided 2.1 ± 1.2 times (range, 1 – 5 times)
116 random spot-urine samples with P/Cr ratio ≥ 0.27 . Dipstick test was positive in 77/83 of
117 specimens with P/Cr ratio ≥ 0.27 , giving a sensitivity of 92.8% for prediction of P/Cr
118 ratio ≥ 0.27 (Table 3). Dipstick test was positive in 28.8% (79/274) of specimens with
119 P/Cr ratio < 0.27 . Thus, the dipstick test overestimated the risk of significant proteinuria
120 in a significant number of specimens. P-test was positive in 68/83 of specimens with
121 P/Cr ratio ≥ 0.27 , giving a sensitivity of 81.9% for prediction of P/Cr ratio ≥ 0.27 (Table
122 3). P-test was positive in 7.3% (20/274) of specimens with P/Cr ratio < 0.27 . Thus,
123 P-test underestimated the risk of significant proteinuria in a significant number of
124 specimens.

125 *Pitfalls in the dipstick test and its screening characteristics for detection of P/Cr ratio \geq*
126 *0.27*

127 Although the dipstick test had a high negative predictive value of 99.5% for “rule out”
128 of proteinuria ≥ 30 mg/dL, it gave a negative test result in 6 (7.2%) of the 83 specimens
129 with a positive result on the P/Cr test (Table 2). As expected, $[Cr]$ was significantly
130 lower in the 6 specimens with a positive test result on the P/Cr test than the 79
131 specimens with a positive test result on the dipstick test but a negative result on the P/Cr
132 test in the absence of a difference in $[P]$ (Table 4). Thus, the dipstick test gave a

133 negative result in the spot-urine specimens with a P/Cr ≥ 0.27 when [Cr] was low,
134 ranging from 25 to 92 mg/dL.

135 *Daily urinary creatinine excretion and completeness of urine collection for 24-h urine*
136 *test*

137 A total of 27 women underwent 64 \times 24-h urine collection. Their pre-pregnancy BMI
138 (mean \pm SD [range]) and volume of 24-h urine ($n = 64$) were 23.0 ± 6.0 [16.6 – 43.3]
139 kg/m² and 2120 ± 885 [489 – 5050] mL, respectively. The distribution of daily urinary
140 creatinine excretion corrected by pre-pregnancy body weight is shown in Fig. 1. When
141 under- and over-collection were defined as levels of urinary creatinine (mg/kg/day) $<$
142 11.0 and > 25.0 , respectively, incomplete urine collection occurred in 10 (15.6%) of the
143 64 \times 24-h urine collection. In analysis of 54 complete specimens with creatinine levels
144 of 11.0 – 25.0 mg/kg/day, daily creatinine excretion was 965.3 ± 159.6 mg, ranging
145 from 702 to 1397 mg/dL, and that corrected by pre-pregnancy body weight was $17.3 \pm$
146 2.9 mg/kg, ranging from 11.7 to 24.9 mg/kg. Thus, although daily creatinine excretion
147 in the urine per day was approximately 1000 mg with a relatively narrow range, [Cr] in
148 the random spot-urine specimens varied widely, ranging from 16 mg/dL to 475 mg/dL
149 (Table 2), suggesting limited clinical value of the P test that determines [P] alone in
150 spot-urine specimens for prediction of significant proteinuria in pregnancy (≥ 0.3
151 g/day).

152 The results of P/Cr test performed within 7 days prior to the 24-h urine tests were
153 available in 39 of the 54 complete 24-h urine tests. One of these 39 tests gave a negative
154 result (< 0.3 g/day), while the remaining 38 tests gave a positive result. However, all
155 P/Cr tests exclusively gave a positive result (P/Cr ratio ≥ 0.27), yielding a sensitivity of
156 100% (38/38) and positive predictive value of 97% (38/39).

157 Aliquots of 5.0 mL of the spot-urine were obtained from 2 women three times during
158 the 24-h urine test. These two cases were determined to have significant proteinuria (\geq
159 0.3 g/day) with 24-h urine test (1.07 g and 0.70 g of protein in the 2860 mL and 2050
160 mL urine with P/Cr ratios of 0.97 and 0.63, respectively). Although [P] varied between
161 3 specimens from the same woman, and 4 of the 6 specimens from the 2 women
162 exhibited [P] < 30 mg/dL, P/Cr test gave a positive test result exclusively in any

163 spot-urine specimen, because [Cr] changed to lower levels with change of [P] to lower
164 levels within a study subject (Fig. 2). Thus, determination of [Cr] in addition to
165 determination of [P] in the spot-urine enhanced the accuracy of detection of significant
166 proteinuria in pregnancy.

167

168 **DISCUSSION**

169 The dipstick used in this study had a low threshold for showing a $\geq 1+$ result; as many
170 as 69 (44%) of 156 spot-urine samples with a $\geq 1+$ test result on the dipstick contained
171 protein < 30 mg/dL (Table 2). As the dipstick should be associated with a low false
172 negative rate (high sensitivity) to avoid missing significant proteinuria, the screening
173 characteristics of the dipstick test used in this study (high sensitivity of 92.8% and a low
174 positive predictive value of 49.4%) for the detection of $P/Cr \geq 0.27$ may have been
175 reasonable. However, dipsticks employed in other countries seem to have higher
176 thresholds than that used in the present study; in comparison with the results of this
177 study, a lower sensitivity ranging from 51% to 60% [4,5] and a relatively higher
178 positive predictive value ranging from 64.9% to 96.9% [2, 3, 6] were reported for the
179 detection of significant proteinuria. An Australian study reported a relatively low
180 positive predictive value of 38% – 60% and a high negative predictive value of 86% –
181 88% [7], similar to the results of this study. As a screening test with low sensitivity
182 gives a high false negative rate, the diagnosis of preeclampsia may be delayed when
183 such a dipstick with a low sensitivity is used. This may explain why proteinuria has
184 been believed to be a late sign in the clinical course of preeclampsia in Western
185 countries [8, 13], whereas we demonstrated previously that significant proteinuria
186 precedes the development of hypertension in approximately 50% of patients with
187 preeclampsia [8, 14].

188 The dipstick test indeed had a low false negative rate (high sensitivity of 98.9%) for the
189 detection of protein concentration ≥ 30 mg/dL in this study. However, it should be kept
190 in mind that the purpose of the urine test is to detect significant proteinuria ≥ 0.3 g/day.
191 As shown in this study, the dipstick test gave a negative test result in a considerable
192 number of specimens with a positive result on the P/Cr test (7.2% [6/83] of specimens).

193 Therefore, care is required in interpretation of dipstick test results. The dipstick test
194 does not take creatinine concentration into account. Determination of protein
195 concentration alone in the spot-urine appears to be used often for the detection of
196 significant proteinuria as an alternative to the 24-h urine test in Japan. However, as
197 demonstrated in this study (Table 3), the absolute value of protein concentration in the
198 spot-urine specimens would be misleading when creatinine concentration is either too
199 high or too low, leading to over- or underestimation of protein loss per day. Creatinine
200 concentration varied largely from 16 mg/dL to 475 mg/dL in the 357 spot-urine
201 specimens in this study (Table 1), thereby leading to varied P/Cr ratio in the presence of
202 a constant protein concentration as shown in Table 4.

203 As daily creatinine production is constant reflecting muscle mass and creatinine is
204 eliminated solely by renal excretion, 24-h urinary creatinine excretion reflects muscle
205 mass, and excretion is relatively constant over time in a given person [15], ranging from
206 11.0 mg/kg/day to 25.0 mg/kg/day [9]. However, urinary creatinine excretion was less
207 than 11.0 mg/kg/day or more than 25.0 mg/kg/day in 10 of 64 24-h urine tests,
208 suggesting that under- or over-collection occurred in these 10 cases. Thus, even the 24-h
209 urine test, which is currently considered the gold standard for determination of
210 significant proteinuria, was often inaccurate, as noted by Côté et al. [9]. Use of the
211 urinary spot P/Cr ratio is currently recommended in evaluation of protein loss per day
212 outside pregnancy [16, 17]. In addition, the Australian Society for the Study of
213 Hypertension in Pregnancy and the International Society for the Study of Hypertension
214 in Pregnancy have proposed use of the urinary spot P/Cr ratio as an alternative to 24-h
215 urine collection [10, 11] and recommend a threshold of 30 mg/mmol (0.265 mg/mg).
216 Therefore, we used a threshold of 0.27 (mg/mg) in this study. Although our
217 investigation on the accuracy of P/Cr test for detection of significant proteinuria (≥ 0.3
218 g/day) was insufficient because of the limited number of women with borderline
219 proteinuria (5 – 30 mg/dL) underwent 24-h urine test, P/Cr test exclusively gave a
220 positive test result in the urine that contained significant levels of protein (≥ 0.3 g/day).
221 According to a systematic review by Côté et al. [12], the P/Cr test has sensitivity of
222 83.6% (95% confidence interval 77.5% – 89.7%) and specificity of 76.3% (72.6% –
223 80.0%) for the detection of significant proteinuria.

224 **This study has some limitations, as follows: this was a retrospective study, multiple**
225 **data from the same subjects were used as independent data, and the fraction of**
226 **women with significant proteinuria was larger in the study population than in the**
227 **general population. These limitations affected our results to some extent regarding**
228 **screening characteristics of Dipstick test and P-test for detecting P/Cr ratio ≥ 0.27 ,**
229 **but did not markedly distort our results “ Dipstick test and P-test were likely to**
230 **over- and underestimate risks of significant proteinuria, respectively” (data not**
231 **shown).**

232

233 In conclusion, a high false positive rate (low positive predictive value of 55.8% in this
234 study) on the dipstick test may explain why we often encounter pregnant women with a
235 negative test result after initially showing a positive test result on a previous antenatal
236 visit. Although an even higher false positive rate is expected in the general population of
237 pregnant women, the dipstick test may be appropriate for screening on the basis of both
238 cost and rapidity. However, it must be remembered that a false negative result may
239 occur when creatinine concentration is very low. Generally, detailed investigation
240 should be offered in women with a positive test result on the screening test. The 24-h
241 urine test is currently an option for women with a positive test result on screening.
242 However, as the 24-h urine test is inconvenient for both pregnant women and obstetric
243 service providers, Japanese obstetricians appeared to hesitate in offering the 24-h urine
244 test. The P/Cr test overcomes this disadvantage. As preeclampsia is a life-threatening
245 complication and the time interval until delivery after diagnosis of preeclampsia is
246 approximately two weeks [8], prompt diagnosis of preeclampsia is important. The P/Cr
247 test may be a useful alternative to 24-h urine test in women with a positive test result on
248 the dipstick test.

249

250 **DISCLOSURE**

251 All authors declare that they have no financial relationship with a biotechnology
252 manufacturer, a pharmaceutical company, or other commercial entity that has an interest
253 in the subject matter or materials discussed in the manuscript.

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- 305
- 306

307 **FIGURE LEGENDS**

308 Fig. 1: Daily creatinine excretion corrected by pre-pregnancy body weight and
309 completeness of urine collection for the 24-h urine test

310 Completeness of 24-h urine collection was defined as creatinine excretion of 11.0 – 25.0
311 mg/kg/day. Three (4.7%) and 7 (10.9%) of the 64 × 24-h urine collections were
312 considered as under- and over-collection, respectively.

313 Fig. 2: Correlation of concentrations between protein and creatinine in spot-urine
314 specimens in two women

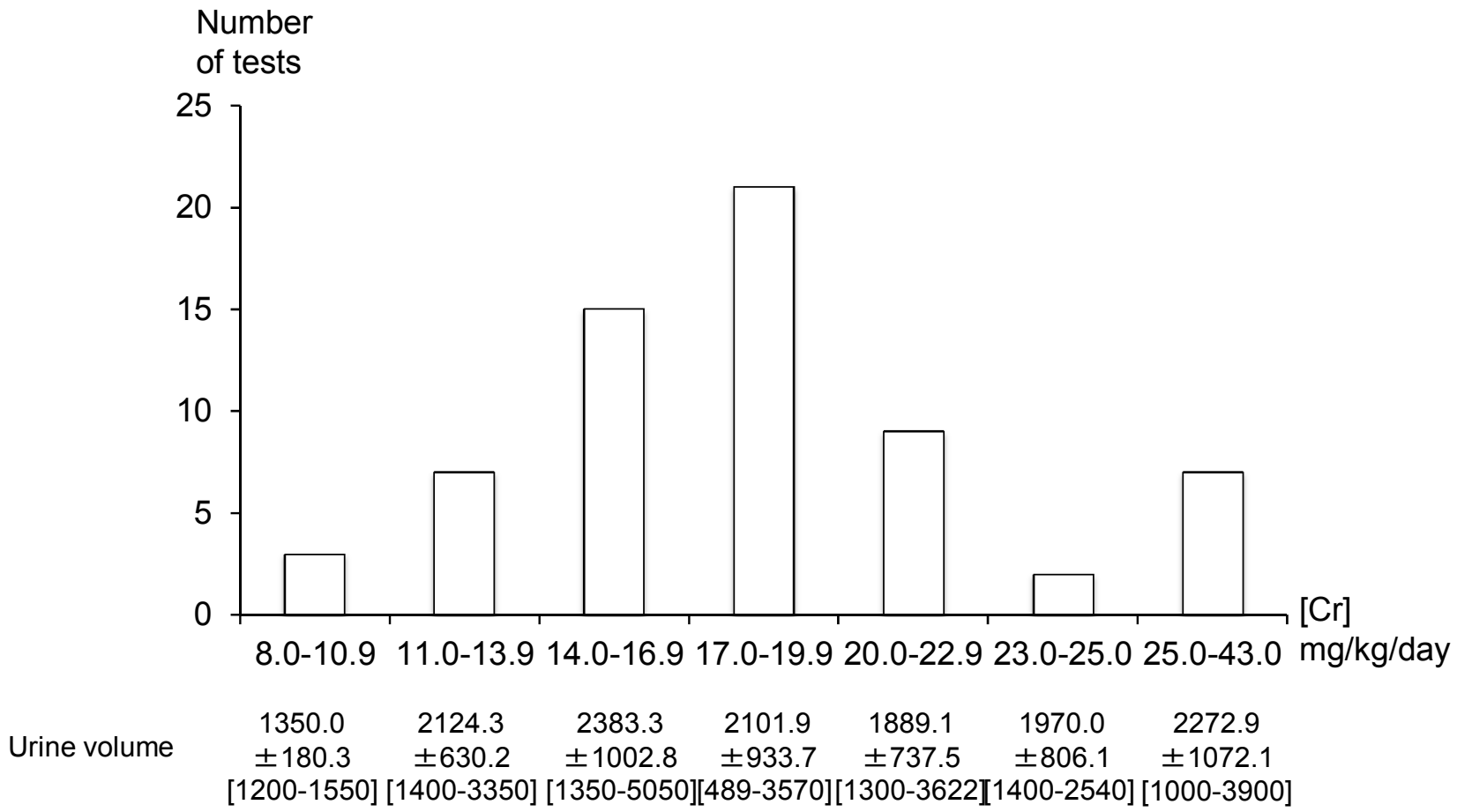
315 The dashed horizontal line indicates a protein concentration of 30 mg/dL. The solid
316 oblique line differentiates the area of P/Cr > 0.27 (upper area) from P/Cr < 0.27 (lower
317 area).

318 Two women (\triangle and \circ) provided an aliquot of 5.0 mL of the spot-urine three times
319 during 24-h urine test before mixture of these 3 spot-urine specimens to the whole 24-h
320 urine collection. These two cases were determined to have significant proteinuria (≥ 0.3
321 g/day) with 24-h urine test (\triangle , 1.07 g of protein in 2860 mL urine with a P/Cr ratio of
322 0.97; \circ , 0.70 g of protein in 2050 mL urine with a P/Cr ratio of 0.63). Protein
323 concentration increased with increasing creatinine concentration in the spot-urine
324 specimens in both women.

325

326

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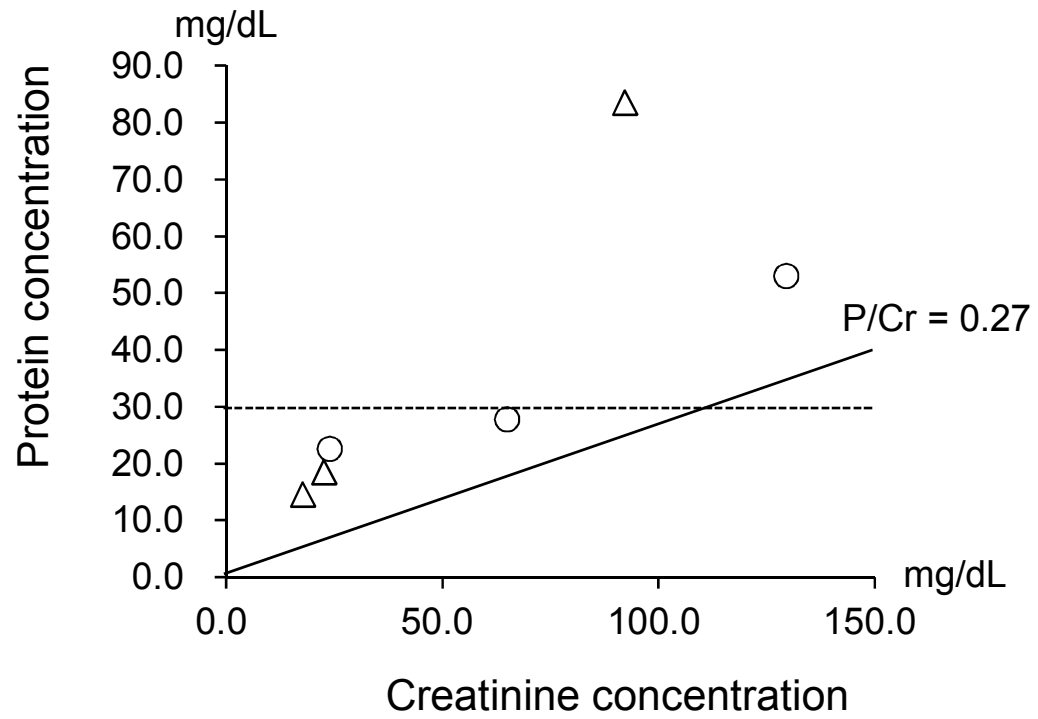


Table 1. Demographic characteristics of 145 study subjects

Age (years)	32.1 ± 4.8
Primiparous	83 (57.2%)
Gestational week at delivery	35.3 ± 4.6
< 37	62 (42.8%)
< 33	32 (22.1%)
Definite diagnosis ¶	
Preeclampsia*	35 (24.1%)
Gestational hypertension	1 (0.7%)
Gestational proteinuria	4 (2.8%)

¶, Diagnosis was made 12 weeks postpartum; * among 35 patients with preeclampsia, 7 showed significant proteinuria defined by a protein to creatinine ratio in the spot urine ≥ 0.27 more than 1 week prior to the development of hypertension.

Table 2: Association between results of dipstick test and concentrations of protein and creatinine in 357 spot urine specimens

	Dipstick test			
	(-)	(+)	(2+)	(≥ 3+)
No. of tests	201	88	34	34
[P] (mg/dL)	3.9 ± 7.1 (0 – 51)	24.2 ± 14.9 (0 – 75)	91.1 ± 55.0 (0 – 217)	289.3 ± 243.9 (0 – 1289)
< 30	200 (99.5%)	60 (68.2%)	4 (11.8%)	5 (14.7%)
30 – 99	1 (0.5%)	28 (31.8%)	16 (47.1%)	4 (11.8%)
100 – 299	0 (0%)	0 (0%)	14 (41.2%)	9 (26.5%)
≥ 300	0 (0%)	0 (0%)	0 (0%)	16 (47.1%)
[Cr] (mg/dL)	80.1 ± 46.4 (16 – 348)	146.6 ± 77.6 (20 – 440)	106.3 ± 87.4 (18 – 383)	123.8 ± 102.8 (22 – 475)
P/Cr ≥ 0.27	6 (3.0%)	22 (25%)	27 (79.4%)	28 (82.4%)

Range is indicated in parentheses.

[P], protein concentration in the urine; [Cr], creatinine concentration in the urine.

P/Cr, protein to creatinine ratio (mg/mg).

Table 3: Screening characteristics of dipstick test and P-test for prediction of protein concentration ≥ 30 mg/dL and/or P/Cr ratio ≥ 2.7

	Target	Sensitivity	Specificity	PPV	NPV
Dipstick test	Protein ≥ 30 mg/dL	99% (87/88) [94-100]	74% (200/269) [69-79]	56% (87/156) [48-64]	99%(200/201) [97-100]
Dipstick test	P/Cr ratio ≥ 2.7	93% (77/83) [85-97]	71% (195/274) [65-76]	49% (77/156) [41-57]	97% (195/201) [94-99]
P-test	P/Cr ratio ≥ 2.7	82% (68/83) [72-90]	93% (254/274) [89-94]	77% (68/88) [65-84]	94%(254/269) [91-97]

PPV, positive predictive value; NPV, negative predictive value.

95% confidence interval is presented in square bracket.

Table 4. Cases with dissociation of results between dipstick and P/Cr tests

Test result		No. of tests	[P] (mg/dL)	[Cr] (mg/dL)	P/Cr
Dipstick	P/Cr				
+	-	79	19.1 ± 11.4 (0 - 42)	172.2 ± 70.4 (20 - 440)	0.11 ± 0.07 (0 - 0.25)
-	+	6	17.2 ± 4.6 (11 - 25)	46.2 ± 24.5* (25 - 92)	0.42 ± 0.14 (0.27 - 0.64)

Range is indicated in parentheses. *, $P = 0.0002$ vs. 172.2 ± 70.4