４．CKD リスク評価式のための尿蛋白/クレアチニン比から尿アルブミン/クレアチニン比への換算

（上記テーマの国際共同研究メタアナリシスへの参画）

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背景：　尿アルブミン/クレアチニン比（ACR）は CKD 病期の主要な要素であり、将来予測の式において重要である。しかし多くのコホート研究では ACR ではなく、尿蛋白/クレアチニン比（PCR）が測定されている。PCR は ACR とは異なるが、ACR への換算が可能と考えられる。

方法：　CKD-PC に参加しているコホートにおいて、PCR と ACR を測定しているコホートのデータを用いて、換算式（直線回帰）を作成した。スプラインを用い、メタアナリシスを行った。

結果：　北米、ヨーロッパ、日本からの 11 コホート、34,708 人のデータを用いた。平均年齢 58 歳、女性 50％、黒人 7.4%であった。ACR 中央値は 181mg/g、PCR 中央値は 373mg/g であった。PCR<50mg/g では ACR との関連はなく、PCR50mg/g 以上では、500mg/g 以上の範囲でやや緩い傾きになった。PCR と ACR の関連はコホート毎に類似しており、メタアナリシスが可能であった。

結論：　ガイドラインでは ACR の測定が勧められているが、ACR を測定していない場合、我々の作成した換算式を用いて PCR からの推定が可能である。

Conversion of urine protein-creatinine to albumin-creatinine ratio for use in CKD risk equations

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Background: Urine albumin-creatinine ratio (ACR) is a core component of CKD staging and used in equations to predict the probability of adverse outcomes. However, many cohorts and health systems preferentially measure urine protein-creatinine ratio (PCR) rather than ACR. These assays measure different protein components and thus are not amenable to harmonization at low levels. On the other hand, higher levels of PCR may be convertible to ACR for use in staging and risk equations.

Methods:　We included cohorts in the CKD Prognosis Consortium with outpatient measures of PCR and ACR performed <90 days of each other, developing an equation for conversion using linear regression. Analyses were performed using all available data within individual cohorts, accounting for multiple records per person, and then meta-analyzed using random effects, using linear splines to model log-PCR with a knot at 500 mg/g.

Results: There were 11 cohorts with 34,708 participants included from North America, Europe, and Japan. Average age was 58 years (SD, 16), 50% were female, and 7.4% were black. Median ACR was 181 mg/g (IQR, 51-304), and median PCR was 373 mg/g (152-654). There was no relationship between ACR and PCR

at PCR <50 mg/g; these values were excluded. Above PCR 50 mg/g, there was a slightly shallower slope at PCR >500 mg/g ($p<0.001$). Relationships between PCR and ACR were similar across cohorts and thus amenable to meta-analysis. (Figure)

Conclusions: Guidelines recommend measurement of ACR. However, when ACR is not available, we developed an equation to convert PCR levels >50mg/g to ACR for use in risk equations.

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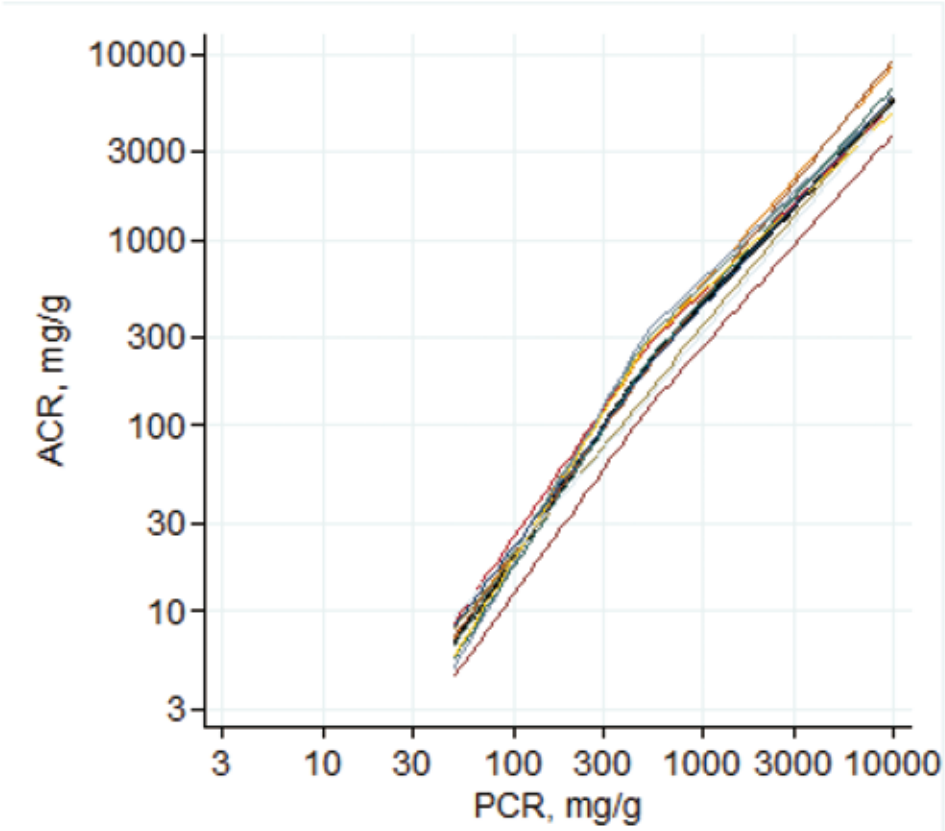
Figure: Relationship between PCR and ACR in 11 studies



ACR=EXP(1.486702*LN(MIN(PCR,500)/200)+1.105372*LN(MAX(PCR,500)/500)+3.99156)

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Background

- Albuminuria is a key factor in the diagnosis, staging, and prognosis of CKD.
- Urine albumin assays were recently standardized, and first morning void urine albumin-creatinine ratio (ACR) is considered a gold standard for albuminuria assessment.
- However, many providers use less precise methods to assess albuminuria such as urine protein-creatinine ratio (PCR) or urine dipstick due to preference or cost considerations.
- The optimal conversion between these methods is not known, nor is the sensitivity and specificity of the less precise methods for the detection of CKD stage A2 and A3.

Methods

- Inclusion criteria: Cohorts in the CKD Prognosis Consortium with measures of urine ACR and PCR or urine ACR and dipstick within 90 days of each other, containing a wide range of urine ACR values
- Study population: Individuals with same-day measures of PCR and ACR; ACR <1 mg/g was excluded.
- Statistical analysis: Linear regression of log-ACR on log-PCR or log-ACR on urine dipstick category within each cohort, followed by random-effects meta-analysis
  - Exposures:
    - PCR was modeled as linear splines with knots at 50, 500 mg/g and was in the range of 20 – 20,000 mg/g
    - Urine dipstick was categorized as negative, trace, 1+, 2+ protein
  - Models: crude and adjusted (sex, diabetes, and hypertension)
    - Other variables (age, race, history of CVD) as well as interactions were tested but were not consistent across cohorts
  - Sensitivity, specificity, positive and negative predictive values were estimated within cohorts for ACR >30 mg/g and ACR >300 mg/g

Results

Table 1: 34 Included Cohorts

Study	N of ACR	ACR (IQI), mg/g	N (%) on same day
AusDiab	22279	5 (3-9)	22279 (100%)
CanPREDDICT	3772	51 (8-449)	3772 (100%)
CRIC	1466	74 (17-427)	799 (55%)
CURE-CKD	3045	156 (31-794)	2996 (100%)
Geisinger	9503	66 (13-418)	3992 (42%)
GLOMMS 2	1304	131 (46-595)	111 (9%)
ICES-KDT	1603638	16 (7-32)	10966 (36%)
IDNT	8888	1167 (486-2363)	8888 (100%)
LCC-CKD	20062	11 (4-33)	19709 (98%)
MASTERPLAN	1704	54 (13-242)	1704 (100%)
Mt Sinai BioMe	5745	195 (23-1000)	4525 (79%)
Nefrona	294	184 (35-648)	294 (100%)
NephroTest	4261	82 (18-417)	4261 (100%)
NIPPON DATA2010	2798	4 (3-9)	2798 (100%)
OLDW center 1	[illegible]	16 (7-44)	283 (34%)
OLDW center 2	42841	18 (8-40)	268 (64%)
OLDW center 3	74259	10 (5-27)	4151 (68%)
OLDW center 4	159638	17 (8-54)	6041 (60%)
OLDW center 5	83116	23 (8-58)	1665 (47%)
OLDW center 6	29584	22 (9-66)	282 (18%)
OLDW center 7	36589	14 (7-43)	723 (26%)
OLDW center 8	29752	18 (7-71)	332 (27%)
OLDW center 9	10262	10 (7-44)	241 (36%)
OLDW center 10	35072	13 (6-48)	1332 (36%)
OLDW center 11	140209	16 (6-70)	12861 (86%)
OLDW center 12	17806	13 (5-54)	462 (41%)
Pima	2471	18 (6-96)	1466 (91%)
PSP-CKD	14193	13 (7-32)	4943 (100%)
RCAV	27909	31 (8-175)	13427 (48%)
RENAAL	3000	1006 (495-2158)	3500 (100%)
SUN-Macro	905	1363 (658-2486)	905 (100%)
Sunnybrook	7361	163 (25-613)	3167 (81%)
Takahata	6995	9 (5-17)	1252 (100%)
West of Scotland	14356	45 (9-375)	12427 (86%)
Total	2488774	16 (8-49)	150255 (76%)

Figure 1: Variation in PCR to ACR Crude Model Across Cohorts

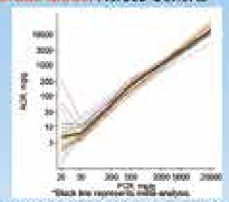
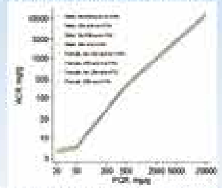


Figure 2: Variation in PCR to ACR Across Covariates in Adjusted Model



PCR Equations

Crude Model:

ACR = exp (0.2756 × log (min (PCR/50, 1)) + 1.5725 × log (max(min(PCR/500, 1) , 0.1)) + 1.1109 × log (max (PCR/500, 1)) + 5.3894)

Adjusted Model:

ACR = exp (0.2445 × log (min (PCR/50, 1)) + 1.5531 × log (max(min(PCR/500, 1) , 0.1)) + 1.1057 × log (max (PCR/500, 1)) + 5.2562 – 0.0793 × (if female) + 0.0802 × (if diabetic) + 0.1339 × (if hypertensive))

Dipstick Equations

Crude Model:

ACR = exp (0.7537 × (if trace) + 1.7346 × (if +) + 3.3624 × (if ++) + 4.6876 × (if >++) + 2.4732)

Adjusted Model:

ACR = exp (0.7370 × (if trace) + 1.6936 × (if +) + 3.2783 × (if ++) + 4.5732 × (if >++) + 1.9911 + 0.0907 × (if female)) + 0.2789 × (if diabetic) + 0.3307 × (if hypertensive))

Table 2: Urine ACR Conversion and Prediction Intervals from Crude and Adjusted Model

PCR (mg/g)	Crude Model	Adjusted Model: Male, No HTN, No DM	Male, No HTN, DM	Male, HTN, No DM	Male, HTN, DM	Female, No HTN, No DM	Female, No HTN, DM	Female, HTN, No DM	Female, HTN, DM
20	5 (2-11)	4 (2-11)	5 (2-11)	5 (2-12)	5 (2-12)	4 (2-10)	4 (2-11)	5 (2-11)	5 (2-11)
50	6 (2-14)	3 (2-15)	6 (2-14)	6 (3-15)	7 (3-15)	3 (2-12)	5 (2-13)	6 (2-14)	6 (3-14)
100	17 (6-46)	16 (5-46)	17 (6-46)	18 (7-49)	20 (6-68)	15 (5-41)	16 (6-44)	17 (6-47)	19 (7-49)
150	33 (12-83)	30 (9-90)	32 (11-92)	34 (12-95)	37 (15-90)	27 (9-82)	30 (10-90)	31 (10-94)	34 (13-88)
200	52 (20-131)	46 (16-138)	50 (19-129)	53 (21-134)	57 (26-128)	43 (15-119)	46 (17-126)	49 (18-131)	53 (22-124)
300	98 (44-219)	87 (34-221)	94 (42-211)	89 (45-221)	107 (54-214)	80 (33-193)	87 (37-205)	92 (39-214)	99 (45-207)
500	219 (112-427)	192 (89-415)	209 (107-405)	219 (113-424)	238 (134-420)	177 (88-365)	192 (94-366)	203 (100-409)	219 (120-402)
700	318 (172-588)	278 (137-564)	301 (164-556)	318 (174-582)	345 (204-583)	257 (133-498)	278 (146-533)	294 (155-558)	318 (183-555)
1000	473 (287-837)	413 (214-797)	447 (252-792)	472 (266-832)	511 (312-837)	381 (207-703)	413 (228-730)	436 (239-794)	472 (280-795)
2000	1022 (622-1678)	888 (497-1586)	962 (581-1583)	1015 (616-1674)	1100 (712-1699)	820 (478-1406)	899 (522-1515)	938 (553-1591)	1016 (642-1609)
3000	1603 (1015-2532)	1390 (815-2383)	1507 (943-2406)	1590 (999-2529)	1722 (1150-2579)	1285 (778-2121)	1362 (848-2283)	1489 (899-2399)	1591 (1036-2438)
5000	2826 (1873-4270)	2448 (1497-3997)	2653 (1730-4061)	2737 (1832-4270)	3030 (2097-4377)	2266 (1431-3569)	2448 (1559-3844)	2583 (1652-4041)	2799 (1897-4130)
Dipstick									
Negative	12 (4-39)	7 (2-22)	10 (3-31)	10 (3-33)	13 (4-46)	8 (3-24)	11 (3-33)	11 (4-35)	15 (3-46)
Trace	25 (6-113)	15 (4-64)	20 (5-80)	21 (5-85)	28 (6-132)	17 (4-67)	22 (5-92)	23 (6-98)	31 (7-134)
+	67 (15-292)	40 (7-225)	53 (11-256)	55 (11-266)	73 (13-312)	44 (9-218)	58 (13-253)	61 (14-262)	80 (21-308)
++	342 (96-1215)	194 (44-868)	257 (65-1014)	270 (70-1050)	357 (101-1384)	213 (53-849)	281 (76-1005)	296 (84-1042)	391 (120-1272)
+++	1262 (385-4135)	709 (176-2866)	937 (253-3472)	987 (270-3611)	1300 (387-4404)	777 (211-2858)	1027 (302-3484)	1081 (322-3628)	1429 (459-4447)

Table 3: Median and Interquartile Interval of Crude and Adjusted PCR Model for detecting ACR 30 and 300 mg/g across cohorts

Cut off at	Crude Model: Sensitivity	Specificity	PPV	NPV	Adjusted Model: Sensitivity	Specificity	PPV	NPV
ACR 30+ Pooled median (IQI)	0.912 (0.886-0.935)	0.840 (0.784-0.892)	0.915 (0.875-0.945)	0.845 (0.778-0.884)	0.917 (0.886-0.940)	0.830 (0.770-0.882)	0.908 (0.871-0.946)	0.850 (0.784-0.885)
ACR 300+ Pooled median (IQI)	0.930 (0.922-0.987)	0.969 (0.955-0.980)	0.964 (0.883-0.948)	0.951 (0.915-0.975)	0.856 (0.836-0.906)	0.967 (0.953-0.979)	0.903 (0.882-0.947)	0.989 (0.905-0.974)

Table 4: Median and Interquartile Interval of Dipstick Values of + and ++ for detecting ACR 30 and 300 mg/g, respectively, across cohorts

Cut off at ACR 30	Dipstick +: Sensitivity	Specificity	PPV	NPV
Pooled median (IQI)	0.456 (0.384-0.550)	0.954 (0.944-0.975)	0.864 (0.824-0.870)	0.798 (0.740-0.815)
ACR 300	**Dipstick ++: Sensitivity**	**Specificity**	**PPV**	**NPV**
Pooled median (IQI)	0.772 (0.691-0.788)	0.976 (0.959-0.984)	0.712 (0.654-0.759)	0.980 (0.974-0.985)

Conclusions

- For PCR >50 mg/g, there is a consistent relationship between PCR and ACR across many cohorts
- Conversion of PCR to ACR or dipstick protein to ACR at the individual level has significant uncertainty
- Predicted ACR can be useful and informative in screening efforts or potentially risk prediction equations such as the kidney failure risk equation, although this requires further testing

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