のエビデンスを与えるものとなった。さらに日本人の心血管疾患を減らして国民全体の生活の質を高めるため、メタボリックシンドロームのみならず包括的なリスクをふまえた対策が必要と考えられる。

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赤坂憲、大西浩文、吉原真由美、三木隆幸、斎藤重幸、三浦哲嗣

第3回臨床高血圧フォーラム
(平成26年5月広島)
各種降圧薬による尿中ACE2排泄量への影響
柴田智、古橋眞人、茂庭仁人、美田知宏、伏屋敬博、石村周太郎、渡邊礼、赤坂憲、大西浩文、吉田英昭、滝沢英毅、齋藤重幸、浦信行、島本和明、三浦哲嗣

第50回日本循環器病予防学会
(平成26年7月京都)
地域一般住民における口腔内健康状態とインスリン抵抗性の関係
藤井瑞恵、大西浩文、赤坂憲、村松真澄、齋藤重幸、三浦哲嗣、森満

第37回日本高血圧学会総会
(平成26年10月横浜)
外来高血圧患者における腎機能低下速度の規定因子
赤坂憲、松本環、吉田英昭、三浦哲嗣

F. 知的財産権の出願・登録状況
(予定を含む)

1. 特許取得:なし
2. 実用新案登録:なし
3. その他:なし

G. 研究協力者

赤坂憲、斎藤重幸、大西浩文、
吉原真由美、三浦哲嗣

厚生労働科学研究費補助金(循環器疾患・糖尿病等生活習慣病対策総合研究事業)
分担研究報告書

地域住民の糖尿病性網膜症頻度をもとに検討した糖尿病診断における血糖関連指標のカットオフ値:久山町研究

研究分担者　清原 裕(九州大学大学院医学研究院環境医学分野・教授)

研究要旨

福岡県久山町の地域住民における糖尿病性網膜症(DR)の有病率調査の成績より、糖尿病診断に対する血糖関連指標のカットオフ値とその有用性を検討した。40～79 歳の住民 2,681 人に 75g 経口糖負荷試験を施行し、空腹時血糖値(FPG)、負荷後 2 時間血糖値(2hPG)、ヘモグロビン(Hb)A1c、グリコアルブミン(GA)、1,5-アンヒドログルシトール(1,5-AG)を測定するとともに、眼科医が DR の有無を判定した。FPG、2hPG、HbA1c、GA、1,5-AG レベルのそれぞれ 10 分位別にみると、DR の頻度はいずれも第 9 分位のレベル(FPG:112～123mg/dL、2hPG:166～224mg/dL、HbA1c:5.9～6.2%、GA:16.2-17.5%)から急峻に上昇した。一方、1,5-AG については第 2 分位(9.6-13.5 μg/mL)以下のレベルで DR の頻度は急上昇した。Receiver operating characteristic(ROC)解析でのカットオフ値は、FPG 117mg/dL、2hPG 207mg/dL、HbA1c 6.1%、GA 17.0%、1,5-AG 12.1 μg/mL であった。さらに 2hPG の ROC 曲線下面積(0.947)は、FPG(0.908)、GA(0.906)、1,5-AG(0.881)より有意に大きく(いずれも $p<0.05$)、HbA1c(0.919)と比べても高い傾向にあった($p=0.07$)。以上の成績より、糖尿病診断における FPG と HbA1c のカットオフ値は現在の診断基準値よりも低く、糖尿病に対する診断能は 2hPG が最も高いことが示唆される。

A. 研究目的

現在の糖尿病の診断基準は、糖尿病網膜症(DR)が出現する血糖値レベルをもとに策定されており、米国糖尿病学会(ADA)や国際保健機構(WHO)は主に欧米人を対象とした疫学調査の成績より、ヘモグロビン(Hb)A1c(NGSP 値)のカットオフ値を 6.5%と定めた。しかし、アジア人を対象としたいくつかの研究では、HbA1c のカットオフ値は異なっており、一致した見解は得られていない。さらに、DR と空腹時血糖値(FPG)、負荷後 2 時間血糖値(2hPG)、グリコアルブミン(GA)、1,5-アンヒドログルシトール(AG)の関連を検討した報告はほとんどない。そこで、本研究では、福岡県久山町の地域住民における DR の有病率調査の成績をもとに、糖尿病診断における FPG、2hPG、HbA1c、GA、1,5-AG のカットオフ値を検討し、その有用性を比較・検証した。

B. 研究方法

2007 年の久山町健診で 40～79 歳の住民 2,681 人(男性 1,192 人、女性 1,489 人)に 75g 経口糖負荷試験(75gOGTT)を行い、FPG、2hPG と HbA1c、GA、1,5-AG を測定した。HbA1c はラテックス凝集反応法を用いて測定し、以下の換算式を用いて JDS 値から NGSP 値に変換した [HbA1c(%)(NGSP 値)=1.02×HbA1c(%)(JDS 値)+0.25(%)]。GA と 1,5-AG の測定は酵素法を使用した。DR は、眼科医による散瞳眼底検査の結果をもとに、単純網膜症、前増殖網膜症、または増殖網膜症が左右いずれかの眼にある場合と定義した。血糖関連指標の各レベルの 10 分位で対象者を 10 群に分け、血糖関連指標と DR の関連をロジスティック回帰モデル、線形回帰モデルを用いて検討した。さらに、ROC 曲線下面積(C 統計量に相当)を用いて、DR を同定するうえでの血糖関連指標の最適なカットオフ値を検討した。

倫理面の配慮

本研究は、九州大学医系地区部局臨床研究倫理審査委員会の承認のもとで行われ、研究に関するインフォ

ームドコンセントを対象者全員から取得した。

C. 研究結果

1. 血糖関連指標のレベルとDRの関係

対象者のうち、52 例に糖尿病網膜症が認められた。血糖関連指標の各レベルの10分位で対象者を10群に分け、DRの有病率を検討した。その結果、図1に示すように、FPG、2hPG、HbA1cおよびGAでは、いずれも第9分位のレベル(FPG:112～123mg/dL、2hPG:166～224mg/dL、HbA1c:5.9～6.2%、GA:16.2～17.5%)からDR の有病率が急峻に高くなった。一方、1,5-AG については、第 2 分位(9.6～13.5μg/mL)以下のレベルでDRの有病率は急上昇した(図 2)。

2. 糖尿病診断における血糖関連指標の最適なカットオフ値

ROC 解析によりDR の存在を判別する上で最適なカットオフ値を求めると、FPGでは117mg/dL(感度82.7%、特異度 86.6%)、2hPG では 207mg/dL(感度 90.4%、特異度 89.3%)、HbA1c(NGSP)では 6.1%(感度 86.5%、特異度88.8%)、GAでは17.0%(感度86.5%、特異度89.0%)、1,5-AG では 12.1μg/mL(感度 78.8%、特異度 85.8%)だった(表)。感度を比べると、2hPG が最も高かった。

3. 最も診断能の高い血糖関連指標は 2hPG

次に、糖尿病診断における判別力を検証するために、血糖関連指標の DR に対する ROC 曲線下面積を比較した。その結果、2hPG の ROC 曲線下面積(0.947)はFPG(0.908)、GA(0.906)、1,5-AG(0.881)より有意に大きく(いずれも $p<0.05$)、HbA1c(0.919)と比べても高い傾向にあった($p=0.07$)(図 3)。一方、FPG、HbA1c、GA、1,5-AG の間で ROC 曲線下面積に有意差は認めなかった。

D. 考 察

日本人地域住民を対象とした本研究の成績では、糖尿病を診断するうえでのFPGとHbA1cのカットオフ値は、現在の診断基準値よりも低いレベルにあった。また、2hPG のカットオフ値は従来の基準とほぼ一致し、その診断能は高いことが示唆された。

① HbA1c のカットオフ値について

我々の検討によると、糖尿病診断に対する HbA1c のカットオフ値は6.1%であった。HbA1cのカットオフ値について、アジア人を対象とした研究はいくつか行われているが、その成績をみると異なった結果が示されている。アジア人種を統合した研究や中国人の研究では、HbA1cのカットオフ値は6.4%、シンガポール人の研究では6.6～7.0%であった。この違いの理由として、本研究の対象者の HbA1c 平均値(5.5%)は他のアジア人(6.0～6.5%)に比べて低いことから、人種・民族間の HbA1c レベルの差が、カットオフ値の違いに影響している可能性が挙げられる。

② GA および 1,5-AG のカットオフ値について

本研究の成績では、GA および 1,5-AG のカットオフ値はそれぞれ 17.0%、12.1μg/mL だった。我々の知る限り、本研究はDRの頻度をもとにGAと1,5-AGの糖尿病診断のカットオフ値を検討した初めての報告である。75gOGTT で判定した糖尿病または糖代謝異常に対するGAのカットオフ値を検討した日本人の報告は2つあり、カットオフ値はそれぞれ 15.5%、17.0%であった。同様の解析を行った報告では、1,5-AG のカットオフ値は14.0～14.2μg/mL であった。これらの成績より、糖尿病診断における GA のカットオフ値は 17.0%付近にあるのに対し、1,5-AGのカットオフ値はこれまでの研究で報告された値よりも低いレベルにあることが示唆される。

③ FPG および 2hPG のカットオフ値について

今回のFPGおよび2hPGのカットオフ値は、それぞれ117mg/dL、207mg/dL であったが、これらの値は、他のアジア人の成績や、我々が過去に報告した成績とほぼ一致していた。つまり、日本人を含むアジア人におけるFPG のカットオフ値は現在の診断基準値よりも低いレベルにあり、2hPG のカットオフ値はほぼ現在の診断基準値に一致すると考えられる。

④ 糖尿病の診断能は 2hPG が最も高い理由

糖尿病の診断能と 2hPG の関係を説明する上で、重要な機序の一つは酸化ストレスである。急激な血糖上昇は慢性的に持続する高血糖に比べ、酸化ストレスをより引き起こすことが知られている。酸化ストレスの亢進はDR 発症と密接に関連していることから、2hPG は DR に対する判別力が高かったと考えられる。

E. 結 論

わが国の一般住民において、FPG、2hPG、HbA1c、GA、1,5-AG の糖尿病診断のカットオフ値はそれぞれ117mg/dL、207mg/dL、6.1%、17.0%、12.1 μg/mL であり、FPG と HbA1c については現在の診断基準値より低いレベルにあった。一方、2hPG は従来の基準とほぼ一致し、その診断能は他の血糖関連指標に比べ高かった。

すなわち、糖尿病診断における FPG と HbA1c のカットオフ値は現在の診断基準値よりも低く、糖尿病に対する診断能は 2hPG が最も高かった。

本研究の結果を検証するため、他の集団においてさらなる検討が必要である。

F. 健康危険情報

特になし。

G. 研究発表

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H. 知的所有権の取得状況

1. 特許取得　　なし
2. 実用新案登録　なし
3. その他　　なし

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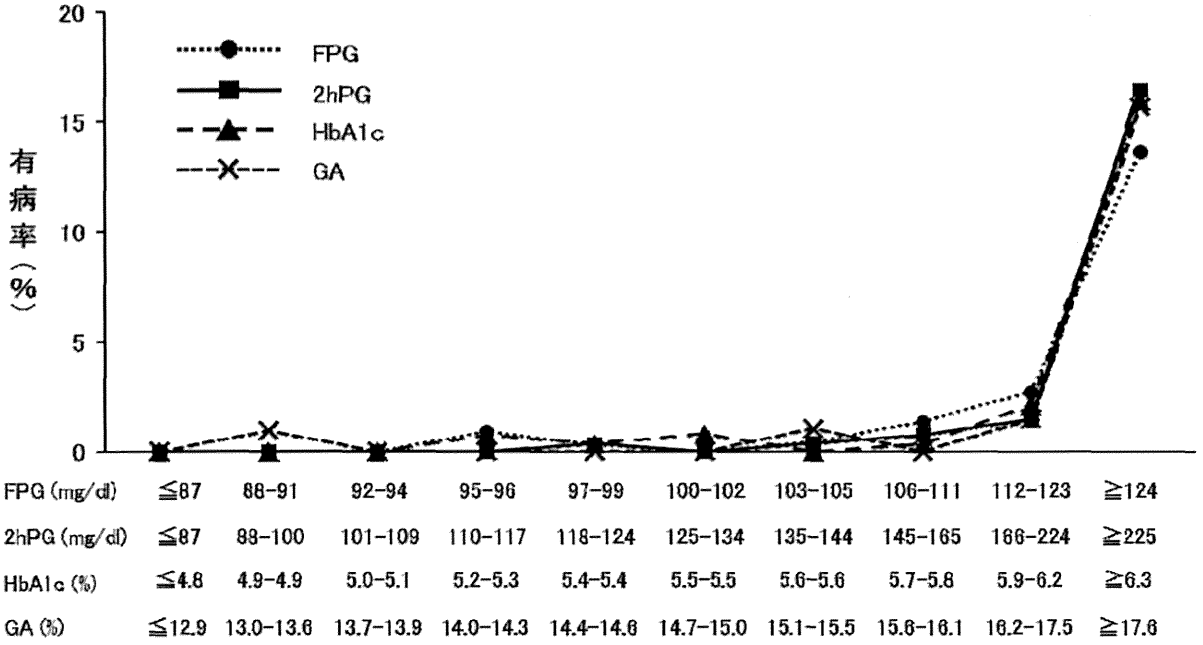


図 1. FPG、2hPG、HbA1c および GA レベルの 10 分位別にみた
糖尿病性網膜症の有病率

FPG: 空腹時血糖値、2hPG: 負荷後 2 時間血糖値、GA: グリコアルブミン

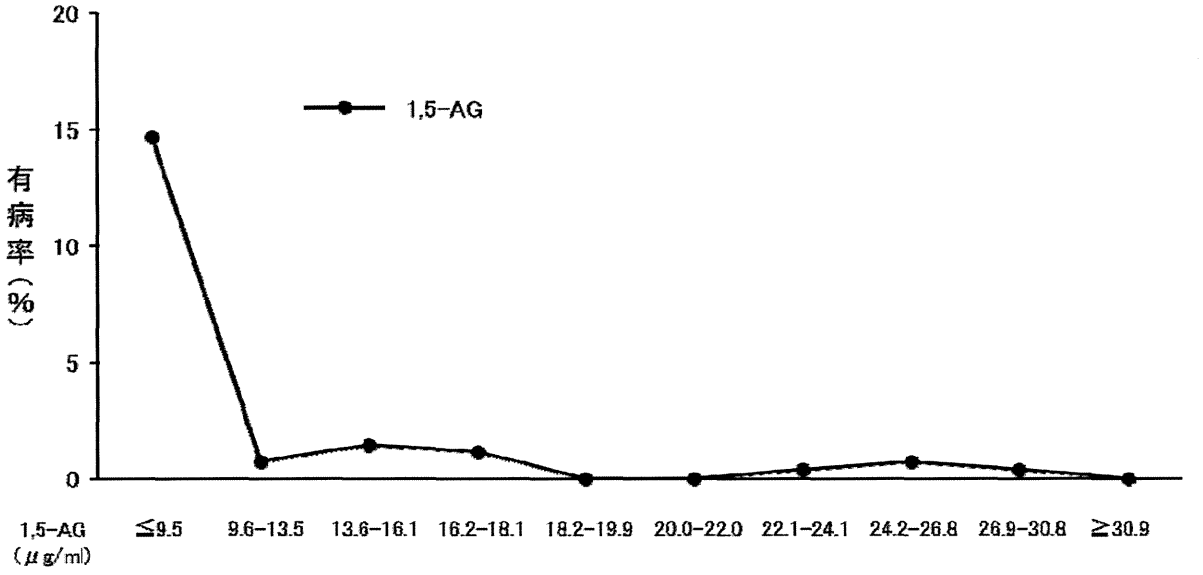


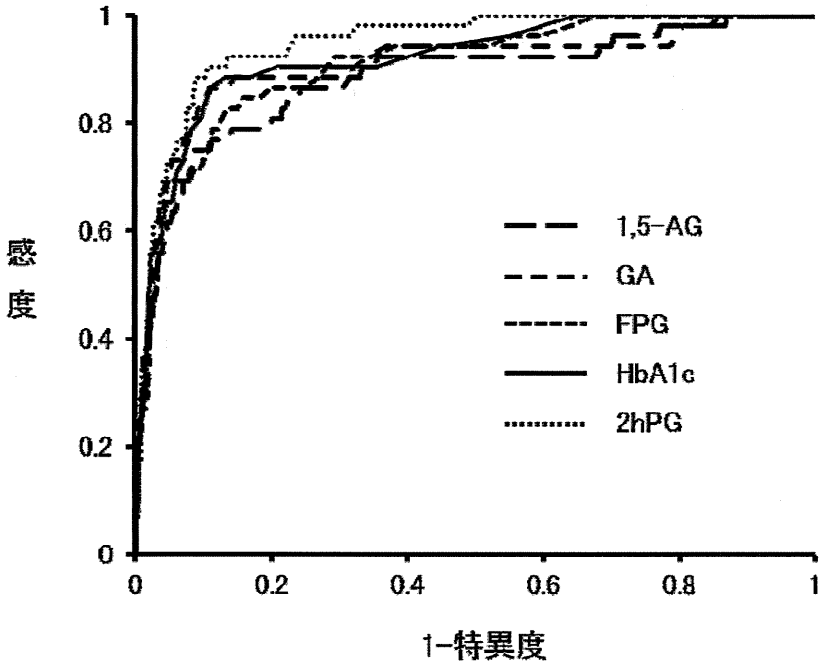
図 2. 1,5-AG レベルの 10 分位別にみた糖尿病性網膜症の有病率

1,5-AG: 1,5-アンヒドログルシトール

表. 糖尿病診断における血糖関連指標のカットオフ値

血糖関連指標	カットオフ値	感度 (%)	特異度 (%)	陽性適中率 (%)	陰性適中率 (%)
FPG	117 mg/dL	82.7	86.6	10.9	99.6
2hPG	207 mg/dL	90.4	89.3	14.3	99.8
HbA1c	6.1%	86.5	88.8	13.3	99.7
GA	17.0%	86.5	89.0	13.5	99.7
1,5-AG	12.1 μg/mL	78.8	85.8	9.9	99.5

FPG: 空腹時血糖値、2hPG: 負荷後 2 時間血糖値、GA: グリコアルブミン
1,5-AG: 1,5-アンヒドログルシトール



血糖関連指標	ROC 曲線下面積 (95%信頼区間)	P 値	P 値	P 値	P 値
1,5-AG	0.881 (0.824-0.937)	基準			
GA	0.906 (0.853-0.960)	0.39	基準		
FPG	0.908 (0.866-0.949)	0.24	0.95	基準	
HbA1c	0.919 (0.878-0.959)	0.22	0.56	0.54	基準
2hPG	0.947 (0.922-0.971)	0.01	0.03	0.01	0.07

1,5-AG: 1,5-アンヒドログルシトール、GA: グリコアルブミン、
FPG: 空腹時血糖値、2hPG: 負荷後 2 時間血糖値

図 3. 血糖関連指標の糖尿病性網膜症に対する ROC 曲線下面積の比較

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書 籍 名	出版社名	出版地	出版年	ページ
清原 裕	Ⅰ.脳血管障害の疫学、社会医学、病型分類 脳血管障害の動向と危険因子の推移	辻 省次 鈴木則宏	アクチュアル脳・神経疾患の臨床 脳血管障害の治療最前線	中山書店	東京	2014	2-8
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原著論文

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分担研究報告書

血漿アルドステロン／レニン比(ARR)低値は全死亡の危険因子

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研究要旨

レニン アンギオテンシン アルドステロンシステム（RAAS）の活性化は、メタボリックシンドローム（MetS）構成因子と強く関連していると考えられている。そこで私達は、そのマーカーである、**血漿アルドステロン(Ald)／レニン比(ARR)と** MetS 等生活習慣病治療の最も重要な指標である死亡との関連を解析した。[方法]山形県高畠町住民検診参加者(2004—2006 年)で、Ald、PRA 共に測定した者 1,310 人（男／女：588/722；年齢：65.9±9.8）を対象に 2011 年末まで追跡した（中央値：2,691 日）。ARR 高値群と低値群にわけ、死亡との関連を Cox 比例ハザード法で、死因別解析には、χ２乗法で解析した。[結果] 1. ARR 低値群は高値群に比して有意に全死亡が多かった(HR:2.33, 95%CI:1.14-4.76)。2. 死因別解析では、ARR 低値群は 高値群に比して、**CVD**（1.83 vs 0.23%, p=0.019)**及び癌**（2.98 vs 0.92%, 0.028)の死亡率が有意に高かった。[結語] ARR 低値は全死亡、一般住民においても、大血管障害死亡のみならず、全死亡の独立した危険因子である。癌死亡の危険因子となっていた。

A. 研究目的

レニン アンギオテンシン アルドステロンシステム（RAAS）は、全身（Systemic）作用としては心血管系に働き血圧調整を行う。また、組織レベルでの（Local）作用も有り、この Local RAAS 系は、肝臓、腎臓、膵臓、脳、血管系、脂肪組織、等の殆どの組織で発現しており、血管造成、細胞増殖、炎症、活性酸素産生等に関与している。従って、RAAS は、Systemic RAS としての大血管障害（CVD）への関与に加えて、local RAS として、癌、糖尿病、肥満、炎症 等の種々疾患、病態と関連すると考えられる。

すなわち、RAAS の活性化は、メタボリックシンドローム（MetS）構成因子と強く関連している。そこで、私達は RAAS のマーカー、血漿レニンの活性(PRA)と MetS 等生活習慣病治療の最も重要な指標である死亡との関連を解析し、PRA 高値が全死亡、CVD 及び癌による死亡の危険因子と成っている事を先の研究にて報告した（Metabolism 2012;61:504)。

今回、この研究を発展させ、RAAS の他のマーカー、アルドステロン(Ald)及び Ald/PRA (ARR)と死亡との関連を一般住民を対象とした追跡調査より検討した。

B. 研究方法

対象：山形県高畠町住民検診参加者(2004—2006年)で、Ald、PRA共に測定した者 1,310 人（男／女：588/722；年齢：65.9±9.8)。追跡調査：死亡、及び、死因を、2011年末まで追跡（中央値：2,691日、64名が死亡)。全死亡の危険因子となるARRのカットオフ値をROC曲線から求め、高値群と低値群にわけ、死亡との関連を

を疑う所見として有名で、ARR >200 が PA のスクリーニング基準として用いられている。では、ARR が低い場合は、問題ないのだろうか？ARR 低値が全死亡、CVD 及び癌死亡の危険因子である事が本研究で示唆された。ARR 低値にも十分な注意を払う必要があると思われた。

Associations between ARR and cause of death-specific mortality

	ARR (n)			At-risk vs. non-at-risk		
	At-risk (613)	Not-at-risk (697)	p (χ^2)	HR	95% CI	p
Total	**48**	**16**	**<0.001****	**2.56**	**1.44–4.56**	**0.001****
Cancer	**21**	**7**	**0.003****	**2.78**	**1.16-6.65**	**0.021***
CVD	**11**	**3**	**0.017***	**3.14**	**0.86-11.48**	**0.084**
Other#	**15**	**6**	**0.023***	**1.81**	**0.69–4.74**	**0.225**

Cox proportional regression analysis was used with adjustment for age and gender. *p<0.05 and **p<0.01. #: Other causes included (n): infections (9), accidents (3), lung diseases (2), brain tumor (2), kidney diseases (1), intoxication (1), suicide (2) and dehydration (1). CVD: cardiovascular disease.

Kaplan-Meier 生存曲線法、Cox 比例ハザード法で、性別、年齢、高血圧治療の有無で補正の上解析した。死因別解析には、χ 2 乗解析を用いた。

C. 研究結果

】1. ARR 低値群は高値群に比して有意に全死亡が多かった（2.33, 1.14-4.76)。2. 全死亡の危険因子となる ARR のカットオフ値を ROC 曲線から求めると、72 となった(AUC: 0.656)。3. 死因別解析では、ARR 低値群は 高値群に比して、CVD (1.83 vs 0.23%, p=0.019)及び癌 (2.98 vs 0.92%, 0.028)の死亡率が有意に高かった。

D. 考察

ARR 高値は原発性アルドステロン症(PA)

E. 結論

ARR 低値は全死亡、一般住民においても、大血管障害死亡のみならず、全死亡の独立した危険因子である。癌死亡の危険因子となっていた。

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H. 知的財産権の出願・登録状況

無

別紙４

研究成果の刊行に関する一覧表レイアウト

書籍(0)

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌（3）

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Daimon M, Konta T, Oizumi T, Kameda W, Susa S, Terui K, Nigawara T, Kageyama K, Ueno Y, Kubota I, Yamashita H, Kayama T, Kato T.	Lower aldosterone-renin ratio is a risk factor for total and cancer death in Japanese individuals: the Takahata study.	Clin Endocrinol (Oxf).	82	489-496	2015
Qi Q,….Daimon M, et al.	FTO genetic variants, dietary intake and body mass index: insights from 177,330 individuals.	Hum Mol Genet.	23	6961-6972	2014
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ORIGINAL ARTICLE

Lower aldosterone–renin ratio is a risk factor for total and cancer death in Japanese individuals: the Takahata study

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Summary

Objective A higher plasma aldosterone–renin ratio (ARR) is an established marker for screening for primary aldosteronism (PA). The association between higher ARR and mortality in a general population has not been fully explored. We here examined whether higher ARR is a risk factor for total and cause-specific mortality in a Japanese population.

Subjects and Methods A population-based, longitudinal study of 1,310 Japanese individuals (age: 63·9 ± 9·8 years) enrolled in the Takahata study between 2004 and 2006 and followed for up to 8 years. The incidence and causes of death were monitored annually until 10 January 2012 (median follow-up: 2691 days).

Results During the follow-up period, 64 subjects died. Kaplan–Meier analysis showed a significantly increased risk for total and cancer mortality in subjects with lower ARR (log-rank $P < 0{\cdot}001$). Cox's proportional hazard model analyses with adjustment for age and gender showed that lower ARR was associated with increased total and cancer mortality in subjects with low (≦72) *vs* high (>72) ARR (hazard ratios and 95% confidential intervals: 2·56, 1·44–4·56 and 2·78, 1·16–6·65, respectively).

Conclusions Lower ARR was a significant and independent risk factor for increased total and cancer mortality in this Japanese population. Subjects with higher ARR were not-at-risk for total death in general. These findings increase the necessity for identifying people with PA from those with higher ARR. People with higher ARR without PA may be at very low risk for total and cancer death.

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Introduction

The plasma aldosterone–renin ratio (ARR) is used to test for primary aldosteronism (PA).[1,2] Although cut-off values to detect such cases vary among studies and medical organizations, people with an ARR above the cut-off value are considered at-risk for PA and undergo confirmatory testing for PA.[1] If confirmatory testing excludes diagnosis of PA, these people are considered to have a higher ARR without PA. This raises the question of whether people with an ARR value similar to those with PA are at-risk for cardiovascular disease (CVD) and/or other adverse conditions.

A person with a higher ARR has either increased aldosterone levels and/or decreased renin levels. In cases with PA, increased aldosterone levels are thought to be responsible for adverse events related to the disease, as aldosterone is reported to promote various effects such as acute endothelial dysfunction, increased collagen deposition with fibrosis, increased vascular tone, and diastolic dysfunction, independent of blood pressure.[3–6] Renin initiates the renin–angiotensin system (RAS), which regulates cardiovascular and electorate homoeostasis systemically. At local levels, RAS promotes multiple physiological functions including tissue angiogenesis, cellular proliferation, apoptosis, generation of reactive oxygen species and inflammation[7–9] and is involved in various pathological conditions such as cancer, liver fibrosis, infection, obesity and diabetes,[7,8,10–12] as well as CVD.[9,13–16] Recently, the association between higher renin levels and total mortality has been reported in a Japanese population.[17] Namely, decreased renin levels seem to be protective against these adverse conditions.

The outcome for a person with a higher ARR seems to be the result of complex interactions between the adverse effects of increased aldosterone and the beneficial effects of decreased renin. In cases with PA, adverse effects may overwhelm beneficial effects, as PA has been reported to have worse outcomes, especially for CVD.[4,6,18,19] With regard to people with a higher ARR without PA, if they are also at-risk for the various conditions as those seen with PA, it is suggested that they should also be treated intensively with aldosterone antagonist

drugs. To investigate this consideration, we conducted a prospective cohort study to examine whether ARR is associated with total mortality in a general Japanese population.

Materials and methods

Subjects

The Takahata study is a population-based cross-sectional study of Japanese people over 40 years old, which was performed to identify possible risk factors for lifestyle-related diseases, such as diabetes and hypertension.[20] Takahata is an agricultural and suburban area about 300 km north of Tokyo. In 2005, among the 26 026 people living in Takahata, 15 357 individuals were over 40. Between 2004 and 2006, 3520 residents were enrolled in the Takahata study. Of these, 1310 (mean age: 63·9 ± 9·8 years; men/women: 588/722) had complete clinical data including their plasma aldosterone concentration (PAC) (pg/ml) and plasma renin activity (PRA) (ng/ml/h) at baseline and participated in the study. The incidence of death was monitored annually until 10 January 2012. There were 64 deaths in this time. The cause of death was determined by reviewing death certificates through to the end of 2011. Causes of death in 2012 were unknown (n = 1). Death certificates of deceased participants were collected with permission from the Management and Coordination Agency of the Japanese Government once yearly. The death code (ICD-10), date and place of death were reviewed. Subjects who moved away during the follow-up period were identified by residence transfer documents (n = 14). The median and maximum durations of follow-up were 2691 and 2760 days, respectively. To further evaluate the association between ARR at baseline and mortality, subjects were stratified into tertiles of ARR (tertiles 1–3: ≤50·0 and ≥118·2, respectively) and into patients at risk (≤72) or not at risk (>72).

This study was approved by the Ethics Committee of the Yamagata University School of Medicine, and written informed consent was obtained from all participants. Blood samples were collected by phlebotomy, mostly between 7 am and 10 am, in a sitting position after at least 5 min rest. PAC and PRA was determined using radioimmunoassay (SPAC-S Aldosterone Kit; TFB Inc., Tokyo, Japan and Renin-RIA bead; Abbot, Tokyo, Japan, respectively). The following clinical characteristics were measured: height, body weight, body mass index, fasting plasma glucose, HbA1c, fasting serum insulin, insulin resistance indexes assessed by homoeostasis model assessment using fasting plasma glucose and insulin levels (HOMA-IR), systolic blood pressure, diastolic blood pressure, serum levels of angiotensin converting enzyme (ACE), total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, total protein, uric acid, urea nitrogen, creatinine, B-type natriuretic peptide (BNP) and adiponectin. HbA_{1c} (%) was measured using the previous Japanese standard substance and measurement method (Japan Diabetes Society (JDS) value) and converted to the National Glycohemoglobin Standardization Program (NGSP) value using the formula: HbA1c (NGSP) = 1·02 × HbA1c (JDS) + 0·25.[21] Diabetes was defined according to 1998 World Health Organization criteria (FPG levels ≥126 mg/dl).[22] In subjects whose FPG levels were not measured, diabetes was defined as a postprandial glucose level ≥200 mg/dl. Subjects with an HbA1c level ≥6·5% were also defined as diabetic as were those on medication for diabetes. Subjects known to have type 1 diabetes were excluded from the study. There were 133 subjects with diabetes. Hypertension was defined as blood pressure ≥140/90 mmHg or being on treatment for hypertension (n = 738). Hyperlipidaemia was defined as total cholesterol ≥240 mg/dl, TG ≥150 mg/dl or being on treatment for hyperlipidaemia (n = 407). Alcohol intake (current or nondrinker) and smoking habits (never, past or current) were evaluated by questionnaire. PA was not defined, as no confirmatory testing for PA was possible as a nature of general health examination.

Statistical methods

The clinical characteristics are given as mean ± SD. The statistical significance of differences in characteristic values between two groups (parametric) and a case–control association between groups stratified by ARR and the incidence of death (nonparametric) were assessed by Student's t-tests and χ^2 tests, respectively. Mortality rates were compared among subjects stratified by ARR using the Kaplan–Meier method. Multivariate Cox proportional hazard regression models were used to calculate hazard ratios (HR) of ARR for mortality with adjustment for factors different between the ARR-at-risk and ARR-not-at-risk groups (e.g. age, sex, medication for hypertension). All analyses were conducted using StatView software version 5.0 (SAS Institute Inc., Cary, NC, USA). Receiver operating characteristic (ROC) curves were plotted to determine the ARR cut-off values to predict the ARR-at-risk group for total death. ROC curves were plotted using GraphPad Prism Version 4.00 for Macintosh (GraphPad Software, San Diego, CA, USA). A P-value <0·05 was considered statistically significant for all analyses.

Results

Baseline clinical characteristics of study subjects

The clinical characteristics of subjects at baseline according to gender are shown in Table 1. Most clinical characteristics, including ARR (P < 0·001), were significantly different between men and women. Therefore, associations between ARR and mortality were evaluated with an adjustment for gender.

Some characteristics, including ARR, were not normally distributed and were highly skewed towards larger values, as previously reported.[17] Therefore, along with serum levels of BNP, adiponectin and PRA, ARR were log-transformed (log10) to approximate a normal distribution. Although PAC was significantly correlated with PRA, the correlation was modest (r = 0·162, P < 0·001) and only a 2·6% change in PAC was explained by that in PRA, indicating that PAC was substantially affected by factors other than PRA. Therefore, ARR appears a consequence of complex interactions among various factors influencing either PAC and/or PRA.

Table 1. Baseline characteristics of study subjects

Characteristics	Men	Women	*P*
Number	588	722	–
Age (yr)	64·6 ± 9·8	63·3 ± 9·8	0·019*
Height (cm)	162·9 ± 6·8	150·8 ± 6·1	<0·001**
Body weight (kg)	62·5 ± 9·6	53·4 ± 8·7	<0·001**
Body mass index (kg/m^2)	23·48 ± 2·95	23·45 ± 3·45	0·872
Plasma Renin Activity: PRA (ng/ml/h)	2·02 ± 2·83	1·22 ± 1·86	<0·001**
Plasma Aldosterone Concentration: PAC (pg/ml)	74·2 ± 35·9	74·6 ± 38·1	0·832
ARR: PAC-to-PRA ratio	113·5 ± 176·9	161·7 ± 195·2	<0·001**
ACE (mg/dl)	15·2 ± 5·3	14·9 ± 5·2	0·328
Serum potassium (mmol/l)‡	4·36 ± 0·43	4·25 ± 0·39	<0·001**
Fasting plasma glucose (mg/dl)†	96·5 ± 16·8	92·3 ± 13·2	<0·001**
HbA1c (%)	5·23 ± 0·68	5·26 ± 0·57	0·570
Fasting serum insulin: IRI (μU/ml)†	5·9 ± 7·0	6·9 ± 11·6	0·094
HOMA-IR†	1·52 ± 3·06	1·68 ± 4·78	0·482
Systolic blood pressure (mmHg)	136·5 ± 15·6	132·3 ± 15·6	<0·001**
Diastolic blood pressure (mmHg)	81·5 ± 10·0	76·4 ± 9·3	<0·001**
Total cholesterol (mg/dl)	191·9 ± 29·8	205·8 ± 30·4	<0·001**
Triglyceride (mg/dl)	112·5 ± 64·0	98·3 ± 45·9	<0·001**
HDL cholesterol (mg/dl)	55·8 ± 14·0	61·2 ± 14·3	<0·001**
LDL cholesterol (mg/dl)	118·2 ± 28·2	127·2 ± 28·9	<0·001**
Serum total protein (g/dl)	7·46 ± 0·46	7·45 ± 0·43	0·925
Serum uric Acid (mg/dl)	5·77 ± 1·27	4·48 ± 1·08	<0·001**
Serum urea Nitrogen (mg/dl)	16·6 ± 4·2	15·9 ± 4·1	0·001**
Serum creatinine (mg/dl)	0·77 ± 0·16	0·59 ± 0·12	<0·001**
BNP (pg/ml)	31·8 ± 48·8	30·7 ± 29·2	0·009**
Adiponectin (mg/dl)	7·5 ± 3·9	11·1 ± 5·4	<0·001**
Hypertension: *n* (%)	356 (60·5)	382 (52·9)	<0·001**
On medication	205 (34·9)	282 (39·1)	0·118
Hyperlipidaemia: *n* (%)	169 (28·7)	238 (33·0)	0·100
On medication	35 (6·0)	92 (12·7)	<0·001**
Diabetes: *n* (%)	69 (11·7)	64 (8·9)	0·087
On medication	41 (7·0)	40 (5·5)	0·284
Drinking alcohol: *n* (%)	426 (72·4)	105 (14·5)	<0·001**
Smoking (Never/Past/Current): *n*	242/170/176	668/17/37	<0·001**

*P < 0·05 and **P < 0·01. Data are mean ± SD or number of subjects (%).
†Data were not obtained from some subjects, most of whom were known to be diabetic prior to examination (*n* (male/female): 564/674).
‡Data were incidentally not obtained from one male subject.

Lower ARR is associated with increased risk of total mortality

Mortality rates among subjects stratified into tertiles of ARR were compared using the Kaplan–Meier method (Fig. 1a). During follow-up, 64 (4·89%) subjects died. Total mortality rates increased significantly as ARR lowered among tertiles (P < 0·001). Cox's proportional hazard regression model analysis used to adjust for age, gender and treatment for hypertension confirmed that lower ARR was associated with increased mortality among tertiles (T1 *vs* T3: 2·33, 1·14–4·76) (Fig. 1b). These results indicated that lower ARR was significantly associated with an increased risk of mortality in the Japanese population.

Association between ARR and mortality is independent of other clinical factors associated with ARR

As is the nature of association studies, it is possible that not ARR itself but other factors associated with ARR may be responsible for the observed association between ARR and mortality. To precisely evaluate this possibility, subjects were divided into two groups, ARR-at-risk (low ARR) and ARR-not-at-risk (high ARR), to determine such confounding factors.

A ROC curve was plotted to determine cut-off values of ARR in relation to total mortality (Fig. 2). In ROC curve analysis, ARR 72 yielded the greatest sensitivity and specificity (75·0 and 54·9%, respectively). The area under the ROC curve (C-index) for ARR was 0·656 (95% CI: 0·594–0·719), while that for PRA was 0·633 (95% CI: 0·563–0·703).

Factors different between the groups were examined (Table 2). Subjects of the ARR-at-risk group were significantly older and had higher fasting plasma glucose and serum levels of potassium, total protein, uric acid, urea nitrogen and creatinine than those of the ARR-not-at-risk group. Proportions of men, smokers and drinkers were significantly greater in the ARR-at-risk group compared with the ARR-not-at-risk group. More subjects of the ARR-at-risk group were on treatment for hypertension and diabetes compared with the ARR-not-at-risk group. Serum adiponectin levels of the ARR-at-risk group were significantly lower compared with the ARR-not-at-risk group. These differences perhaps suggest why the ARR-at-risk group is at higher risk for total death, although lower systolic blood pressure and serum BNP levels observed in the ARR-at-risk group compared with the ARR-not-at-risk group seem to be contradictory.

We next examined associations between the ARR-at-risk group with total death using Cox proportional hazard regression analysis, which revealed the ARR-at-risk, age, gender, serum levels of uric acid, creatinine and BNP, drinking alcohol and smoking as associated with total death in the univariate analyses. Multivariate Cox proportional hazard regression analysis using all these factors as covariates showed a significant independent association of the ARR-at-risk group (HR: 2·58, 95% CI: 1·42–4·69) with total death (Table 3).

Association between ARR and cause-specific mortality

The association between ARR and cause of death-specific mortality was then examined (Table 4). Cause of death varied and the total number of deaths was relatively low in this period. Therefore, we grouped causes of death into the following categories: cancer (n = 28), CVD (n = 14), other [infections (n = 9), accidents (n = 3), lung diseases (n = 2), kidney diseases (n = 1), intoxication (n = 1), suicide (n = 2), dehydration (n = 1)] and

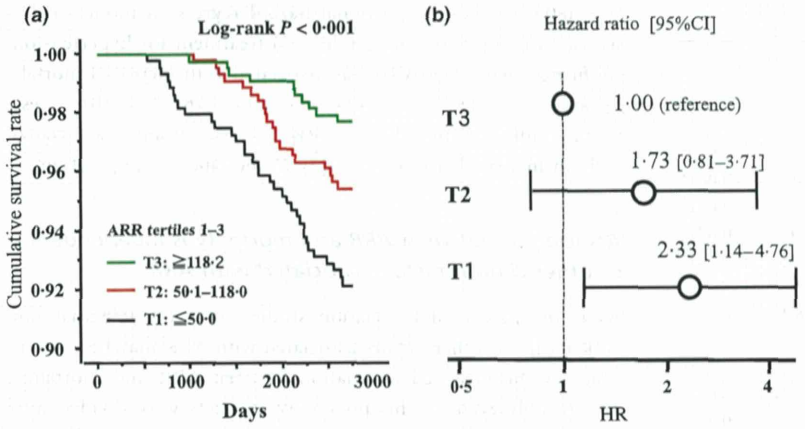

Fig. 1 Kaplan–Meier survival curves (a) and hazard ratios (b) for the tertiles of ARR. The significances of the differences among the groups were assessed using log-rank tests and Cox proportional regression analysis adjusted for age, gender and medication for hypertension. The *P*-values are indicated on each panel. A *P*-value <0·05 was considered statistically significant.

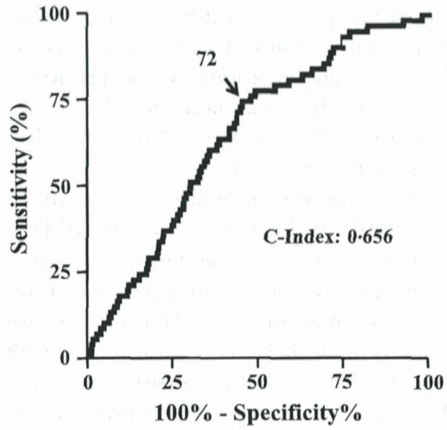

Fig. 2 Receiver operating characteristic (ROC) curves for the determination of cut-off values of ARR as a predictor for the risk of total death. An arrow indicates cut-off value yielding the greatest sensitivity and specificity (75·0 and 54·9%, respectively).

unknown ($n = 1$). As shown in Table 4, the rates of death caused by cancer (3·43 *vs* 1·00%, $P = 0·003$), CVD (1·79 *vs* 0·43, $P = 0·017$) and other (2·45 *vs* 0·86, $P = 0·023$) were significantly higher in the ARR-at-risk group than in the ARR-not-at-risk group.

We next examined the association between ARR and cause of death-specific mortality using a Cox proportional hazard regression analysis with adjustment for age and gender, which further confirmed the independent association between ARR and cancer mortality (HR: 2·78, 95% CI: 1·16–6·65), and marginally confirmed the association between ARR and CVD mortality (HR: 3·14, 95% CI: 0·86–11·48). An association between ARR and death caused by other means was not confirmed (HR: 1·81, 95% CI: 0·69–4·74), and an association between the specific causes of death in this category was not determined.

Discussion

As RAS is involved in various pathological conditions, PAC, PRA and therefore ARR are expected to be associated with a range of clinical characteristics. ARR appeared to be affected by various factors, which may confound the association between ARR and total mortality observed in the study. We examined factors associated with ARR and used all associated factors as covariates to examine independent associations between ARR and total mortality. This analysis clearly showed that lower ARR is a risk factor for total death in this Japanese general population independent of such factors. This finding suggests that lower ARR should not be ignored. A higher ARR indicates an increased possibility of PA, while a lower ARR indicates a higher mortality.

The results seem to indicate that subjects with higher ARR are not-at-risk for total death in this general population. As we did not segregate those with PA from those without, the results were a mixture of the consequences of these two populations. However, as the study subjects appear to represent the general population (as one factor of the study design), and the prevalence of PA has been reported to be at highest 10–15% in hypertensive populations,[1,2,23,24] we believe that the results represent the consequences of subjects with higher ARR without PA. As PA has been established as a risk for CVD and mortality,[1,24] the results may suggest that those with higher ARR are not at risk for total death, provided that they do not have PA. Subjects with very high ARR may possibly represent those with PA. However, even the top decile stratified based on ARR (ARR ≥324) was found as associated with total death with decreased total mortality (HR: 0·31, 0·07–1·42, $P = 0·130$) similar to the ARR-not-at-risk group. Contrary, we tried to exclude possible subjects with PA from those with higher ARR. Such subjects were defined as those with hypokalaemia (≤3·5 mmol/l) and ARR ≥200, and exclusion of them ($n = 8$) further increased the HR of the significant independent association of the ARR-at-risk group with total death from 2·58 to 2·81. This result seems to further support the above-mentioned idea. The results strengthen the importance of diagnosing people with PA from those with higher ARR because people without appear not to be at risk or have better outcomes compared with those with lower ARR.

Activation of RAS is associated with increased CVD risk in many intervention studies in which hypertensive patients were treated with RAS inhibitors (e.g. ACE inhibitors and/or

Table 2. Differences in baseline characteristics of study subjects stratified by ARR risk for total death

Characteristics	At-risk	Not-at-risk	*P*
Number	613	697	–
ARR: PAC-to-PRA ratio	36·6 ± 18·9	231·1 ± 221·1	<0·001**
Plasma Renin Activity: PRA (ng/ml/h)	2·77 ± 3·04	0·53 ± 0·36	<0·001**
Plasma Aldosterone Concentration: PAC (pg/ml)	68·2 ± 33·5	79·9 ± 39·3	<0·001**
Gender (M/F)	342/271	246/451	<0·001**
Age (year)	64·1 ± 10·1	63·7 ± 9·6	0·445
Height (cm)	157·4 ± 8·7	155·3 ± 8·8	<0·001**
Body weight (kg)	58·0 ± 10·0	57·0 ± 10·3	0·093
Body mass index (kg/m^2)	23·34 ± 3·18	23·57 ± 3·28	0·199
ACE (mg/dl)	14·8 ± 5·7	15·2 ± 4·8	0·118
Serum potassium (mmol/l)‡	4·33 ± 0·43	4·27 ± 0·40	0·008**
Fasting plasma glucose (mg/dl)†	96·0 ± 15·9	92·6 ± 14·2	<0·001**
HbA1c (%)	5·25 ± 0·67	5·22 ± 0·58	0·345
Fasting serum insulin: IRI (μU/ml)†	6·4 ± 4·8	6·4 ± 4·8	0·928
HOMA-IR†	1·55 ± 1·23	1·66 ± 5·50	0·630
Systolic blood pressure (mmHg)	132·9 ± 16·1	135·4 ± 15·3	0·006**
Diastolic blood pressure (mmHg)	78·3 ± 10·4	79·1 ± 9·5	0·135
Total cholesterol (mg/dl)	199·5 ± 32·5	199·6 ± 29·4	0·972
Triglyceride (mg/dl)	105·4 ± 58·5	104·1 ± 52·1	0·678
HDL cholesterol (mg/dl)	59·0 ± 14·9	58·5 ± 14·1	0·531
LDL cholesterol (mg/dl)	123·4 ± 30·1	123·0 ± 27·9	0·831
Serum total protein (g/dl)	7·52 ± 0·48	7·40 ± 0·41	<0·001**
Serum uric Acid (mg/dl)	5·31 ± 1·41	4·84 ± 1·22	<0·001**
Serum urea Nitrogen (mg/dl)	16·5 ± 4·1	15·9 ± 4·2	0·007**
Serum creatinine (mg/dl)	0·70 ± 0·17	0·65 ± 0·15	<0·001**
BNP (pg/ml)	28·9 ± 46·0	33·3 ± 32·0	<0·001**
Adiponectin (mg/dl)	9·1 ± 4·7	9·8 ± 5·4	0·0496*
Hypertension: *n* (%)	349 (56·9)	389 (55·8)	0·683
On medication	248 (40·5)	239 (34·3)	0·021*
Hyperlipidaemia: *n* (%)	196 (32·0)	211 (30·3)	0·507
On medication	57 (9·3)	70 (10·0)	0·650
Diabetes: *n* (%)	72 (11·7)	61 (8·8)	0·073
On medication	47 (7·7)	34 (4·9)	0·037*
Drinking alcohol: n (%)	294 (48·0)	237 (34·0)	<0·001**
Smoking (Never/Past/Current): *n*	384/114/115	526/73/98	<0·001**

*$P < 0·05$ and **$P < 0·01$. Data are mean ± SD or number of subjects (%).

†Data were not obtained from some subjects, most of whom were known to be diabetic prior to examination (*n* (risk/not-at-risk): 583/655).

‡Data were incidentally not obtained from one subject of the ARR-at-risk group.

angiotensin II type I receptor blockers).[13,25,26] Associations between RAS and cancer have been reported in many epidemiological and intervention studies, most of which showed that RAS activation was associated with the incidence and/or progression of cancer.[7,8,27–29] However, the effects of RAS inhibitors on cancer risk are inconsistent.[7,8,27–31] However, the RAS is expected to be associated with cancer, as the RAS is known to regulate various physiological functions related to cancer such as angiogenesis, invasion, pro-survival signalling and proliferation, which have been reported in various *in vitro*, animal and clinical studies as dysregulated in malignancy.[7,8] To date, the effects of RAS activation on the risk of CVD or cancer in the general population have not been fully clarified. We previously reported on the association of higher PRA with CVD and cancer mortality in the general population.[17] In the current study, we examined whether ARR is also associated with CVD and cancer mortality and revealed a significant association between ARR and cancer mortality, and a marginal association with CVD mortality after adjustment for age and gender using Cox proportional hazard regression analysis. These results strengthen the suggestion that associations between RAS and cancer as well as CVD are clinically relevant.

In this study, we examined the association between ARR and mortality. ARR has been reported as a better test for screening cases of PA compared with PAC and PRA and is being used commonly in ordinary clinical settings.[1,2] Whether ARR is also a better test for predicting mortality has not been clarified. To evaluate the issue, we examined the association between PAC and PRA with mortality. Cox's proportional hazard regression model analysis with adjustment for age and gender showed a U-shaped association between PAC (HR of tertiles 3 and 1 *vs* tertile 2 were 1·34, 0·69–2·59 and 1·45, 0·79–2·65, respectively) and a linear association between PRA and total mortality [higher PRA was associated with increased mortality among tertiles (T3 *vs* T1: 1·83, 0·93–3·60)]. However, these associations were not significant. Furthermore, PRA appears less useful for determining risk groups than ARR because ROC curve analysis showed that the area under the ROC curve for PRA was smaller than that for ARR. The results indicate that ARR is a better means to predict mortality compared with either PAC or PRA.

Although associations between ARR and mortality have not been well examined, one study with Caucasian patients with heart failure reported that subjects who died from CVD had lower ARR compared with survivors.[32] This study aligns with our results. However, a recently published Japanese study reported possibly conflicting results with our own. In that study, although no association between ARR and stroke was found, higher ARR was reported to be associated with the incidence of stroke in those with a higher sodium intake stratified into halves by median sodium intake (10·5 g/day).[33] The reasons for the differing results cannot be explained precisely at present. It is possible, however, that differences in study populations, time when was blood drawn, and subjects fasting or not may be contributing factors. In the conflicting study, the researchers excluded people on medication for hypertension, the proportion of which was about 25% of people who gave informed consent to participate. It is therefore possible that the study subjects represented a nonhypertensive population rather than the general population. Additionally, subjects had blood taken in the non-fasted state, and in both the morning and afternoon. PAC and

Table 3. Hazard ratios for total death

	Univariate			Multivariate		
Characteristics	HR	95%CI	*P*	HR	95%CI	*P*
ARR-at-risk group (*vs* not-at-risk groups)	3·45	1·99–6·16	<0·001**	2·65	1·48–4·75	0·001**
Age(per 1 year)	1·10	1·07–1·14	<0·001**	1·09	1·05–1·13	<0·001**
Gender (M *vs* F)	4·51	2·49–8·16	<0·001**	1·71	0·74–3·96	0·213
Medication for hypertension (*vs* none)	1·52	0·93–2·48	0·097		NA	
Diabetes (*vs* nondiabetes)	1·46	0·72–2·95	0/294		NA	
Medication for diabetes (*vs* none)	1·30	0·52–3·23	0·579		NA	
Height (per 1 cm)	1·01	0·98–1·03	0·678		NA	
Systolic blood pressure (per 1 mmHg)	1·01	0·99–1·02	0·302		NA	
Serum potassium (per 1 mmol/l)†	1·44	0·86–2·41	0·168		NA	
Serum total protein (per 1 g/dl)	1·00	0·58–1·74	0·998		NA	
Serum uric Acid (per 1 mg/dl)	1·28	1·07–1·52	0·006**	1·00	0·82–1·22	0·968
Serum urea Nitrogen (per 1 mg/dl)	1·02	0·96–1·08	0·580		NA	
Serum creatinine (per 1 mg/dl)	7·23	3·37–15·48	<0·001**	2·35	0·58–9·59	0·233
BNP (per 10 × log pg/ml)	1·13	1·06–1·20	<0·001**	1·07	0·99996–1·14	0·0501
Adiponectin (per 10 × log mg/dl)	1·06	0·95–1·18	0·322		NA	
Drinking alcohol (None *vs* yes)	0·40	0·24–0·66	<0·001**	0·62	0·33–1·17	0·141
Smoking (Past *vs* current)	1·14	0·58–2·23	0·708	0·82	0·41–1·61	0·555
(Never *vs* current)	0·40	0·22–0·73	0·003**	0·56	0·29–1·10	0·094

Cox proportional regression analysis was used with all variables listed above as covariates.
*$P < 0·05$ and **$P < 0·01$. NA: not appreciated as covariates.
†Data were incidentally not obtained from one subject.

Table 4. Associations between ARR and cause of death-specific mortality

	ARR (n)			At-risk vs. not-at-risk		
	At-risk (613)	Not-at-risk (697)	*P* (χ^2)	HR	95% CI	*P*
Total	48	16	<0·001**	2·56	1·44–4·56	0·001**
Cancer	21	7	0·003**	2·78	1·16–6·65	0·021*
CVD	11	3	0·017*	3·14	0·86–11·48	0·084
Other†	15	6	0·023*	1·81	0·69–4·74	0·225

Cox proportional regression analysis was used with adjustment for age and gender.
*$P < 0·05$ and **$P < 0·01$.
†Other causes included (n): infections (9), accidents (3), lung diseases (2), brain tumour (2), kidney diseases (1), intoxication (1), suicide (2) and dehydration (1). CVD: cardiovascular disease.

PRA changes upon dietary intake and PAC are known to decrease in the afternoon with circadian rhythms.[34] The amount of dietary salt consumption could also account for the discordance. Unfortunately, we do not have these data from our study sample. However, the median dietary salt consumption has been reported as 12·44 g/day in the same study area,[20] which is higher than that reported for the conflicting report's sample, and therefore does not seem to account for the discordance. Finally, as an association between ARR and lower mortality has been reported in Caucasian populations, we believe that the results are general across ethnicities, although further studies with increased population sizes of different ethnicities are needed.

The mechanisms for why those with higher ARR but without PA are not at risk for total death cannot be clearly explained. Such subjects appear to have increased PAC and decreased PRA as those with PA, and should therefore be at similar risk for CVD, or eventually for total death. This hypothesis does not appear correct from the results of the current study. The values of PAC may be less in those with higher ARR but without PA than in those with PA, although both groups have higher ARR. PAC has been reported to change with circadian rhythms.[34] Those with higher ARR but without PA appear to have normal PAC circadian rhythms, as such people were generally considered as normal subjects. However, some people with PA have perturbed PAC circadian rhythms.[35] These differences in circadian rhythms may contribute to the different outcomes observed between people with higher ARR but without PA and those with PA, as is the case in people with Cushing syndrome, in which not only absolute but also chronically elevated cortisol levels were suggested for the adverse outcomes. The above-mentioned

possibilities are merely speculative, however, and require further examination.

Antihypertensive drugs have a substantial influence on RAS. ACE inhibitors, angiotensin II type I receptor blockers and mineralocorticoid receptor antagonists decrease PAC, increase PRA by a feedback mechanism and can decrease ARR. Some diuretics and beta-blockers also increase PRA, while calcium channel blockers have no influence. Direct renin inhibitors, such as aliskiren, inhibit PRA. Direct renin inhibitors were only recently approved for clinical use in Japan; therefore, no subjects were on the drugs at baseline. The classes of antihypertensive drugs used appeared to be confounding factors in analysis. We evaluated the influences of antihypertensive treatment on the association between ARR and total mortality without regard to the class of drug used. This is a limitation of the study. Cox's proportional hazard model analysis with adjustment for factors related to ARR including age and gender showed no significant association between medication for hypertension and total mortality ($P = 0{\cdot}983$). Therefore, although the class of drug used was not considered, medication for hypertension did not seem to have a substantial influence on the results.

A further limitation is that blood samples were collected in the sitting position after at least 5 min rest, which does not appear sufficient to overcome the large variability in the influence of posture on PRA, and thus ARR. A strength of the study is that statistical adjustments were made for multiple factors that could possibly confound the results, and a population-based/general sample of individuals was used.

In conclusion, we found that lower ARR was significantly and independently associated with an increased risk for total and cancer mortality in a general Japanese population. Lower ARR indicated higher mortality, while higher ARR indicated a higher possibility of PA. This finding suggests that diagnosing people with PA from those with higher ARR is extremely important, as those without seem to have better outcomes compared not only with those with PA but also those with lower ARR. This finding requires further evaluation using an increased population size and participants from different ethnicities.

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Disclosures

Nothing to disclose.

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