

が、糖尿病を基礎疾患にもつ高齢者では積極的にインフルエンザワクチン、肺炎球菌ワクチンの接種を受けるべきであり、糖尿病例に対する感染予防の重要性についての説明が必要である。

## ●おわりに

糖尿病例は、健常者に比し感染症の重症化や難治化をきたしやすい。さらに、感染症に罹患することにより血糖コントロールが悪化して糖尿病状態が進行する悪循環が繰り返される。糖尿病例は早期からの適正な血糖コントロールと併せて、感染症合併を予防することが重要である。重症感染症の発症を契機に、入院時に初めて糖尿病を診断される症例も散見されるので、常に感染症、糖尿病の両病態の関連性を考慮に入れて日常診療にあたるべきである。

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患者における感染症の特徴及びその対策. 糖尿病 50:137-143

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「診断の達人」「鑑別診断の神様」と呼ばれる、米国を代表する内科医、ローレンス・ティアニー氏による「診断入門」の第2版。「診断の原則と実際の進め方」をわかりやすく示すことで絶賛された初版に、大幅な加筆を加え、さらに内容を充実させた。まさに「診断入門書」の決定版であり、これを読まずして「診断」を語ることはできない。

## 超高齢者における白衣高血圧治療の効果 —HYVET 試験サブ解析の結果より—

Does white coat hypertension require treatment over age 80? : Results of the hypertension in the very elderly trial ambulatory blood pressure side project.  
Bulpitt CJ *et al* : *Hypertension* 61 : 89-94, 2013

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### はじめに

診察室血圧 (clinic blood pressure : CBP) は必ずしも自由行動下血圧 (ambulatory blood pressure : ABP) を正確に反映するものではない。両者の差は、診察室であるがゆえに生じる警戒心によって左右され、個人差、測定方法、同席者などによっても異なる。診察室での警戒反応は患者の年齢とともに増加し、慣れとともに減少する。CBP が正常値を上回り、ABP が正常である場合、白衣高血圧と定義される。従来、白衣高血圧に対しては、積極的な降圧薬治療は不必要とされてきた。これは、積極的な降圧薬治療によっても白衣高血圧例の ABP は低下せず、また心血管イベントも抑制されることはないと思われてきたからである。本研究では、80 歳以上の超高齢者高血圧に対する大規模介入降圧薬臨床試験のサブ解析として、積極的治療群とプラセボ投与群とのあいだで ABP と CBP を比較し、HYVET 試験に参加した患者における白衣高血圧の割合あるいは積極的治療の意義を検討した。

### 対象と方法

対象は HYVET 試験参加者 3,845 例のうち ABP データを有する 284 例である。HYVET 試験のプロトコールについては、参加者は年齢が 80 歳以上で、2 ヶ月以上のプラセボ導入期間後の収縮期 CBP の平均が 160 mmHg から 199 mmHg かつ常時 140 mmHg 以上の例を対象とした。積極的治療群には降圧目標である収縮期 CBP 150 mmHg 未満および拡張期 CBP 80 mmHg 未満を達成するため、まずインダパミド徐放剤 (利尿薬) を 1.5 mg/日の投与、必要があればペリンドプリル (ACE 阻害薬) を毎日 2 mg/日または 4 mg/日の追加投与がおこなわれ、またはプラセボ投与群には同時期にプラセボが投与

された。ABP データを有する 284 例のうち 112 例は投薬前の基礎値 ABP データを有し、186 例は治療中の ABP データを有し、このうち 50 例は両時期の ABP データを有していた。日中の ABP は午前 8 時～午後 8 時のあいだに記録された (超高齢者のなかには就寝時間が早い患者がいるため終了時間を午後 8 時と定めた)。夜間測定は午後 10 時～午前 6 時のあいだに記録された (超高齢者は睡眠時間が短い傾向があるため、午前 6 時と定めた)。CBP と日中 ABP の比較、さらに 90% の参加施設が CBP を午前中に測定しているため、CBP と午前中 ABP (午前 8 時～正午 12 時のあいだに記録) の比較をおこなった。

白衣高血圧は収縮期 CBP が 140 mmHg 以上 (全参加患者がこれに該当した) で、日中収縮期 ABP が 135 mmHg 未満および拡張期 ABP が 85 mmHg 未満と規定された。

### 結果

降圧薬 (またはプラセボ) 投与前では、24 時間 ABP の平均値は 133/77 mmHg であり、夜間 ABP の平均は 124/72 mmHg であった。CBP と日中 (午前 8 時～午後 8 時) ABP の差の平均は収縮期血圧で 36 mmHg (範囲 -13～+73 mmHg)、拡張期血圧で 12 mmHg (範囲 -31～+35 mmHg) であった。患者のほぼ全員 (97%) について、収縮期 CBP が日中 ABP よりも高く、80% の患者について拡張期 CBP が日中 ABP よりも高かった。CBP と午前中 (午前 8 時～正午 12 時) ABP を比較した場合、平均差は収縮期血圧で 32 mmHg (範囲 -33～+80 mmHg)、拡張期血圧では 10 mmHg (範囲 -35～+41 mmHg) であった。90% の患者において収縮期 CBP が午前中収縮期 ABP よりも高く、76% の患者において拡

表 1. ABP サブスタディ参加者と HYVET 試験参加者の特徴的な基礎値

	投薬前の基礎値 ABP	治療中の ABP	全 ABP	HYVET 参加者
年齢	82.9±2.6	83.7±3.6	83.4±3.4	83.5±3.2
女性	72 (64.9%)	124 (66.0%)	162 (65.3%)	2,327 (60.5%)
収縮期座位	172.0±8.0	175.3±9.7	174.2±9.2	173.0±8.5
拡張期座位	90.0±9.5	91.3±8.9	90.9±9.4	90.8±8.5

表 2. プラセボ群と積極的治療群の平均 13カ月の ABP の結果

	座位 CBP	午前 ABP	日中 ABP	24 時間 ABP
収縮期血圧 mmHg				
プラセボ	162 (19)	159 (18)	133 (17)	131 (17)
積極的治療	146 (18)	144 (18)	126 (18)	123 (18)
差	17	16	8	8
拡張期血圧 mmHg				
プラセボ	86 (11)	85 (11)	80 (11)	77 (10)
積極的治療	78 (11)	78 (11)	74 (10)	72 (10)
差	7	6	6	5

張期 CBP が午前中拡張期 ABP よりも高かった。降圧薬（またはプラセボ）投与前では、日中 ABP 基準とした場合 56 例（50%；95%信頼区間は 40~60%）の患者が、午前中 ABP を基準とした場合は 43 例（38%；95%信頼区間、29~48%）の例が白衣高血圧を示した（表 1）。表 2 は治療群別（積極的治療群とプラセボ群）の CBP および ABP の結果を示すものであり、積極的治療またはプラセボ投与開始から 13ヵ月後の記録である。プラセボ群と積極的治療群との治療中 CBP の差は 17/7 mmHg であった。日中 ABP のプラセボ-積極的治療間の差は 8/6 mmHg であった。24 時間 ABP の差は平均 8/5 mmHg であった。

## 考 察

HYVET 本体試験（3,845 例）では、80 歳以上高血圧高齢者（CBP が 160~199 mmHg）に対する 2 年間のインダバミド+ペリンドプリルによる積極的降圧薬治療により 21%の死亡率減少、30%の脳卒中発症抑制、34%の脳卒中発症抑制が認められた。プラセボ群と積極的治療群との CBP の差は、本体試験では 15/6 mmHg であり、今回のサブ試験では 17/7 mmHg と、本体試験と比較しても遜色のないものであった。

今回のサブ試験の結果は、HYVET 試験の対象患者のうち 40~60%には白衣高血圧があったこと示唆する。従来、白衣高血圧は治療を必要としないとされていたが、もし積極的薬物治療の効果が本体試験のごとく大きいものであれば、そのおよそ半数は白衣高血圧の参加者から得られた結果となる。白衣高血圧の有病率は加齢とともに

に上昇し、今回の結果から白衣高血圧例の多数には治療がおそらく効果的であると考えられる。近年の ABP 測定データベース解析によると、平均 60 歳の孤立性収縮期高血圧例での白衣高血圧の有病率は 28.6%であり、未治療白衣高血圧例全体では正常血圧例とくらべ心血管リスクに有意差は認められない（ $p=0.29$ ）ものの、層別解析では男性および糖尿病合併白衣高血圧例ではより大きな心血管リスクを有することが報告されている。今回の解析により、超高齢者の白衣高血圧例には治療が有効であることが示唆されるが、超高齢者層における白衣高血圧の定義そのものの変更が必要である可能性があり、今後無作為抽出試験によるより詳細な解析が必要である。収縮期血圧が高齢者の心血管疾患罹病率と死亡率への重要な関与要因であることや、家庭血圧測定も白衣高血圧の診断にも役立つことを心にとどめておかねばならない。

## 展 望

インダバミド徐放剤+ペリンドプリル治療の有効性につき超高齢者においては CBP と ABP の意味づけに乖離を認めたことから、高齢者にとって白衣高血圧は良性ではなく、24 時間 ABP の収縮期圧が 125 mmHg 以上の 80 歳以上の患者には治療が必要である。

英国国立臨床研究所のガイドラインでは、白衣高血圧には治療は不必要との立場をとるが、根拠となった臨床研究ではいずれも平均年齢が 56~63 歳の比較的若年層の白衣高血圧例を対象としており、80 歳以上の白衣高血圧例にはあてはまらない可能性がある。この議論を追求するにはさらに無作為抽出試験が必要となる。

## 乾癬と高血圧

The association between psoriasis and hypertension : a systematic review and meta-analysis of observational studies.

Armstrong AW *et al* : *J Hypertens* 31 : 433-443, 2013

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### はじめに

乾癬は世界人口の2~4%にみられる慢性の炎症性皮膚疾患である (Christophers E : *Clin Exp Dermatol* 26 : 314, 2001). 近年の疫学的研究は、乾癬が高血圧の有病率と罹患率に大きく関与することを示唆している。乾癬と高血圧の疫学的関係の正確な機序は明らかでないが、高血圧は心血管危険因子の一つであることから (Chobanian AV *et al* : *Hypertension* 42 : 1206, 2003), 乾癬例をスクリーニングすることは有用である。本研究は、乾癬と高血圧の関係をよりよく理解するために、観察研究のシステマティック・レビューとメタ解析をおこなった。

### 対象と方法

1980年1月1日~2012年1月1日のあいだに発表された論文のうち、英語言語と、ヒトを対象とした研究に限定し、MEDLINE, EMBASE, Cochrane Central Register のデータソースを用いて、システマティック・レビューをおこなった。すべての論文の要約を読み返し、症例対照、断面調査、コホートまたはケース・コントロール比較試験のいずれかで、乾癬または乾癬性関節炎と関連した高血圧の評価、対照群と乾癬または乾癬性関節炎例との比較をおこなっており、診断コード、請求書コード、臨床医診断、患者自己報告、血圧測定、またはカルテレビューにより高血圧の罹患率と有病率の評価を得られるとの基準を満たすすべての論文を抽出した。最初の系統的調査により80の要約を得て、そのなかから47の論文の全文すべてを調査した。このうち、24の論文が乾癬のメタ解析に適合し、5つが乾癬性関節炎のメタ解析に適合した。研究の質を評価するために、6ポイントスケールを適用した。出版バイアスは、ファンネル・プロットの日視試験とBeggの順位相関係数試験を用いて評価した。研究の異質性検定により特定された変数と変量効果メタ解析を用いて、乾癬コホートのメタ回帰を実行した。

### 結果

本研究では、上記試験基準を満たす合計およそ270万人の試験参加者となる24件の乾癬の観察研究を調査した。このうち、309,469例が乾癬であった。論文の多くは、乾癬例のあいだで高血圧の有病率を報告した後ろ向き症例対照研究、または横断研究であった。乾癬例の高血圧有病率のメタ解析により、研究間の重要な異質性が明らかとなった ( $I^2=98.4\%$ )。症例対照と断面研究の変量効果モデルにもとづいて検定した。乾癬例における高血圧罹患のオッズ比 (OR) は、対照群と比較して1.58 [95%信頼区間 (CI) 1.42~1.76] であった。軽症乾癬例における高血圧罹患のORは1.30 (95% CI 1.15~1.47) であり、重症乾癬例の高血圧罹患のORは対照群と比較して1.49 (95% CI 1.20~1.86) であった (図1)。

高血圧の罹患率を調査した2つのコホート研究では、乾癬が高血圧罹患に対しOR1.09 (95% CI 1.05~1.14) および1.17 (95% CI 1.06~1.30) の寄与度で関与していることが明らかとなった。サブ解析において乾癬性関節炎例では、より高い高血圧罹患率を示すことが明らかとなった (OR 2.07, 95% CI 1.41~3.04) (図2)。出版バイアスはいずれの研究でも認められなかった ( $p=0.7$ )。

### 考察

本研究では、多くの観察研究で乾癬と高血圧との有意関係を認めた。一般例と比較して、乾癬例では高血圧のより高い有病率と罹患率が認められた。有病率研究からの調査結果にもとづくメタ解析は、一般例とくらべて、乾癬例では高血圧が1.58倍高いことがわかった。また、乾癬例のサブ解析では、軽症乾癬例と比較して、重症乾癬例が高血圧に対しより大きく関与していた。乾癬と高血圧は、肥満や喫煙など共通の危険因子を有するが、ほとんどの研究はこれらの危険因子で補正した後も、独立有意関与を示した。乾癬の高血圧への有意関与に関しその基盤となる正確な機序は明らかではない。考えうる機

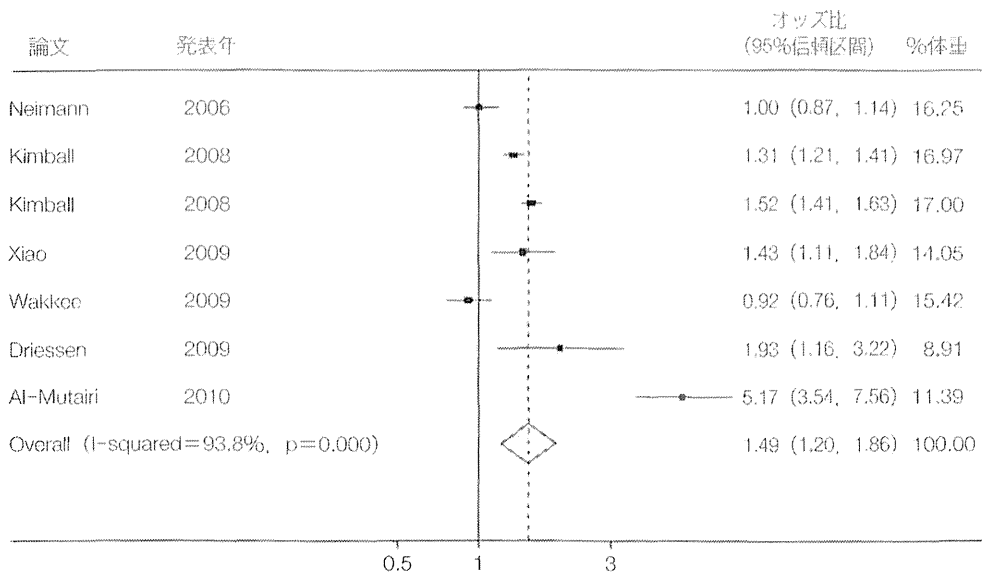


図 1. 重度乾癬患者における高血圧有病率のメタ解析

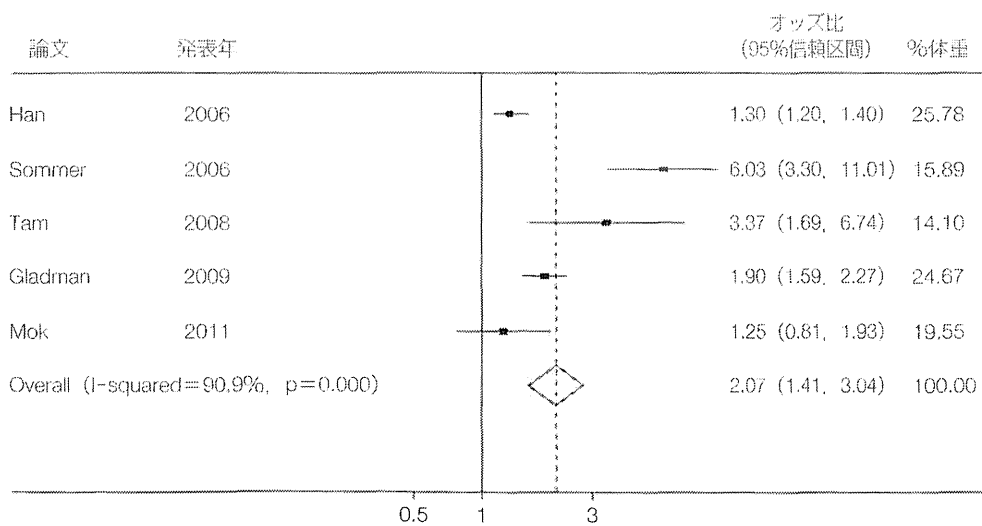


図 2. 乾癬性関節炎患者における高血圧有病率のメタ解析

序としては、第一に、乾癬例での血圧調節機構におけるレニン・アンジオテンシン (RA) 系の異常である。乾癬例では、血漿レニン活性およびアンジオテンシン変換酵素活性の高値が報告されており、これら RA 系の異常は乾癬例におけるサイトカイン調節異常に中心的な役割を果たしている可能性がある。第二に、乾癬例の血清および病変皮膚中でのエンドセリン-1 の上昇が知られており、エンドセリン-1 は強力な血管収縮物質であることから、乾癬例における高血圧の有病率上昇に関与している可能性がある。第三に、乾癬例では体内各種酸化ストレス物質が増加していることが知られており、これら酸化ストレスを介して内皮細胞の血管拡張機序が損なわれて

いる可能性がある。

**おわりに**

本研究では、観察研究のシステマティック・レビューとメタ解析により、乾癬が高血圧の有病率と罹患率増加に独立有意関与因子となっていることを明らかにした。乾癬の高血圧への関与の詳細機序を解明し、乾癬と高血圧重症度の関連を解明し、高血圧管理における乾癬の系統的治療法を明らかにするため、更なる研究が必要である。いずれにせよ、乾癬例および乾癬性関節炎例において、積極的に高血圧および他の心血管危険因子のスクリーニングがおこなわれなければならない。

## 5. 高齢者救急

森本 茂人

**要約** 高齢者人口の増加から、高齢者救急患者は今後急増することが予想される。看取りも含めた在宅医療や、医療と介護の連携の習得とともに、急性期病院での救急医療、これに続く地域への退院支援をも含めて一体の高齢者医療システムとしての医学教育プログラムの展開が必要である。高齢者では救急対応が必要な急性疾患であっても、症状や経過が非定型的であることが多く、個人差も大きいことから、高齢者救急の現場で必要とされる検査の習得が必要である。また、高齢者救急例では、原因となる急性疾患以外にも、多臓器の合併症発症の予防、治療が必要とされ、恒常性維持機構易破綻、薬物副作用にも注意する。さらに治療に際しては輸液や循環器薬使用の習熟が必須である。病態や患者が置かれている社会的状況も考慮して個々に治療ゴールの設定が必要となる。

**Key words** : 高齢者, 救急医療

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### 高齢者で救急対応が必要な急性期疾患

高齢者の救急対象となる疾患では、脳卒中、急性冠症候群、肺炎、急性腹症などに対する診断、救急搬送基準、治療に習熟する必要がある。以下に要点を示す。

#### 1) 脳卒中

①一過性脳虚血発作も含め、疑いがあれば、速やかに脳卒中急性期医療機関へ搬送する。

②診断には画像検査(特に拡散強調画像)が望ましい。

③発症直後の降圧療法は高血圧性脳症やくも膜下出血以外は病型診断後でよい。

④一過性脳虚血発作も脳梗塞に準じて重要に扱う。ABCD<sup>2</sup>スコアを参照<sup>1)</sup>。

⑤75歳以上での血栓溶解療法は適応を慎重に判断する。

⑥急性期から合併症予防に取り組む。

#### 2) 急性冠症候群(ACS)

①ST上昇型急性ACSだけでなく、非ST上昇型ACSでも中等度リスク以上であれば、速やかに循環器急性期医療機関へ搬送する。

②高齢者では、無痛性ACS、せん妄や失神で初発するACSにも注意する。

③トロポニンTを測定する。

#### 3) 急性腹症

①腹痛が制御できない場合は、速やかに消化器対応急性期医療機関へ搬送する。

②高齢者においても、腹部大動脈瘤破裂、腸間膜動脈血栓症、絞扼性イレウス、消化管穿孔、胆嚢穿孔、ヘルニア嵌頓、結腸軸捻転など緊急手術を要する疾患に注意する。

#### 4) 肺炎

成人市中肺炎診療ガイドライン(2007年日本呼吸器学会)では下記の身体所見、年齢による重症度分類(A-DROPシステム)を採用している<sup>2)</sup>。本邦では意識レベルはJapan Coma Scale(3-3-9度方式)が用いられる。ただし、高齢者ではI・1~3程度の意識レベルは認知症などで日頃から存在する場合があります。肺炎に由来する意識障害であることを検討する必要がある。

### 高齢者救急の現場で必要とされる検査

高齢者救急例では、まずは気道確保、ショック、嘔吐への対応が必要である。また意識レベル、バイタルサイン(呼吸、脈拍、血圧、体温)、SpO<sub>2</sub>測定を繰り返し観察する。高齢者救急例では、症状が非定型的であり、また合併症も多発することから、全ての救急例に対して、血算(含、血小板、Neutro%), CRP, Na, K, BUN, Cr, CK, CK-MB, LDH, T.Bil, アルブミン、血糖、HbA1c、

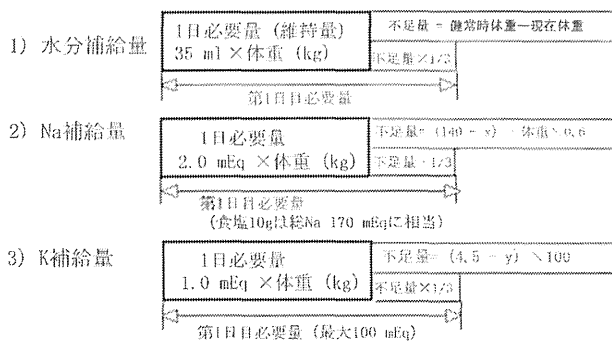
Emergency medicine for the elderly

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表1 高齢者救急に必要情報

- ◆まずは気道確保、ショック、嘔吐への対応
- ◆意識レベル、バイタルサイン（呼吸、脈拍、血圧、体温）、SpO<sub>2</sub>測定を繰り返し観察。
- ◆全ての救急例に対して  
血算（含、血小板、Neutro%）、CRP、Na、K、BUN、Cr、CK、CK-MB、LDH、T.Bil、アルブミン、  
血糖、HbA1c、BNP、心電図
- ◆疑う疾患には集中して

疑い疾患名	診断に必要な検査
急性冠症候群	トロポニンT、心エコー
重症不整脈	心エコー、心電図モニター
心不全急性増悪	心エコー、中心静脈圧、胸部CT、SpO <sub>2</sub> 、PaCO <sub>2</sub>
脳卒中、頭蓋内疾患	頭部CT、MRI：特にDWI
肺炎	PaCO <sub>2</sub> 、Neutro%、胸部Xp、胸部CT、痰培、結核を除外
播種性血管内凝固症候群（DIC）	血小板、FDP、フィブリノゲン、PT、AT-III
敗血症	血液培養2連検、エンドトキシン、β-Dグリカン
急性腎不全（脱水・DIC・薬剤）	eGFR（血清クレアチニン、年齢、性）、尿酸
消化管出血	潜血（便：吐物）、血算、BUN/Cr、腹部Xp：CT：エコー
急性腹痛	腹部Xp：CT：エコー：MRI
大動脈解離	血圧左右差、胸部Xp（縦隔拡大）、単純CT、造影CT
高血圧緊急症	レニン活性、アルドステロン、カテコラミン
肺塞栓症	Dダイマー、心エコー、造影CT、肺シンチグラム、肺動脈造影



x=現在の血清Na値、y=現在の血清K値

図1 維持量および欠乏量の計算

BNP、心電図検査を行う。また、疑われる疾患には集中して特殊検査を行う（表1）。救急の現場では必要最小限の検査に留める。不要な検査を多数行うことは結果的には診断を遅らせる。

### 輸液に対する基本知識の習得

高齢者救急例においては、経口摂取が不能または禁忌となり輸液が必要となる例が多く、輸液に関する基本的知識の習得が必要である。まずは、輸液の種類と適応、特に細胞外液補充液、1~4号輸液の特性と特徴に関する知識は是非とも必要である。また、水、Na、Kにつき、維持量と欠乏量が計算できることが必要である。

### 1) 輸液の種類と適応

①細胞外液補充液：血漿と電解質濃度がほぼ同じ組成を持つ。Na欠乏型脱水（出血、嘔吐、下痢による脱水）、ショックに適用。生理食塩水、リンゲル液、乳酸加リンゲル液など。

②1号液（開始液）：Kイオンを含んでいないのが特徴。緊急時などの病態不明時の水分・電解質補給の第一選択薬。通常1本のみ使用し、病態が判明すれば他の輸液に移行する。

③2号液（脱水補給液）：細胞内に多い電解質（K<sup>+</sup>、Mg<sup>2+</sup>、HPO<sub>4</sub><sup>2-</sup>）を含むのが特徴。利尿がついた後の低カリウム血症や細胞内電解質が不足する脱水に用いられる。

④3号液（維持液）：水分・電解質の1日必要量が組成の基準。経口摂取不能または不十分な患者の水分・電解質の補給と維持に用いられる。

⑤4号液（術後回復液）：電解質濃度が最も低く、水分の補給を目的とした輸液。腎機能の未熟な新生児や小児、腎機能が低下している高齢者や術後早期の患者に用いられる。

### 2) 維持量および欠乏量の計算（図1）

輸液の水、電解質（特にNa、K）の維持量（1日単位で計算）、欠乏量（総量で計算、1日補給量はその1/3、3日間かけて補正）の計算は日常的に行えることが必要である。維持量に関しては、水分補給量は35ml×体重（kg）、Na補給量は2.0mEq×体重（kg）、K補給量

表2 高齢者救急で使用頻度の高い循環器用薬

対象疾患	薬剤名	商品名	用量	摘要
心不全	フロセミド	ラシックス	初回 10-20 mg 静注, 持続静注は 2.5 mg/時	反応尿量確認 (300-1000 ml/2- 数時間), 不応時 (重症, 腎機能低下, 低 Alb 血症) は他剤, 血圧低下, 低 K に注意.
	ドバミン	イノバン等	2-10 $\gamma$ 持続静注	腎血流量増加作用. ( $\geq 5 \gamma$ で昇圧作用)
	ミルリノン	ミルリーラ	初回 50 $\mu$ g/kg 静注, 0.25-0.75 $\gamma$ 持続静注	心筋細胞内の cAMP 濃度上昇
	カルベリチド	ハンブ	0.0125-0.2 $\gamma$ 持続静注	利尿作用 (hANP)
高血圧緊急症	ニカルジピン	ペルジピン	0.5-6 $\gamma$ 持続静注	脳卒中急性期は過降圧に注意
	ジルチアゼム	ヘルベッサ	5-15 $\gamma$ 持続静注	脳卒中急性期は過降圧に注意
	ニトログリセリン	ミリスロール	5-100 $\mu$ g/分持続静注	脳卒中急性期は過降圧に注意
心室頻拍・心室細動	リドカイン	リドカイン オリバス	初回 1-1.5 mg/kg, 追加 0.5-0.75 mg/kg, 最大 3 mg/kg, 静注	電氣的除細動で復帰しても頻回到再発するとき
	アミオダロン	アンカロン	初回 150-300 mg, 3-5 分後に追加 150 mg, 静注	電氣的除細動で復帰しても頻回到再発するとき
頻脈性心房細動	ベラパミル	ワソラン	5 ~ 10 mg, 静注.	2 分以上で (WPW 症候群には禁忌)
	ジルチアゼム	ヘルベッサ	0.25 mg/kg 静注.	2 分以上で (WPW 症候群には禁忌)
	ジゴキシン	ジゴシン	0.125-0.25 mg, 2 時間毎総量 1 mg まで, 静注.	上記 2 剤に不応時, または心不全時 (LVEF < 40%). (WPW 症候群には禁忌)
心房細動 (48 時間以内)	基礎疾患のある心房細動では電氣的徐細動を優先. 心機能に問題のない発症 48 時間以内の除細動には下記の Na <sup>+</sup> チャンネル遮断薬による除細動を試みる.			
	ビルジカイニド	サンリズム	1 mg/kg まで静注	血圧・心電図監視下で 10 分か.
	シベンゾリン	シベノール	1.4 mg (0.1 ml)/kg 静注	血圧・心電図監視下で 5 分以上かけ.
	ジソピラミド	リスモダン P	50 ~ 100 mg 静注	5 分以上かけゆっくり
	フレカイニド	タンボコール	1 ~ 2 mg/kg, 静注 総投与量は 150 mg まで	血圧・心電図監視下で 10 分か. 三環系抗鬱薬の併用で QRS 幅延長, 心室頻拍
	プロカインアミド	アミサリン	総量は 17 mg/kg	20 mg/分で静注
心房細動	48 時間以上持続している場合には原則として 3 週間以上の抗凝血薬療法が必須であり, さもなければ経食道心エコーによって左房内血栓が否定されてから除細動を行うことが推奨される.			
	ヘパリン	各種	5,000 U ボーラス後 14,000 U/日 持続静注	塞栓予防
	ワーファリン	ワーファリン	0.5 mg-5.5 mg/日 経口	塞栓予防, PT-INR 1.6-2.5 に調節
房室ブロック	めまいや失神, 呼吸困難等の症状血行動態の悪化を伴う場合は不安定と判断し, 根治的には経皮ペースング~経静脈ペースングを準備する. ペースングの準備中に, アトロピン, アドレナリン, ドバミン, イソプロテレノールを使用する.			
	アトロピン	アトロピン	0.5 mg を 3 ~ 5 分ごと, 総投与量 0.04 mg/kg まで	狭隅角緑内障/尿閉に注意. Mobitz 2 型 II 度房室ブロックでは使用せず, 以下の投薬. 不応時は経皮ペースング施行.
	アドレナリン	ボスミン	2 ~ 10 $\mu$ /分, 持続静注	1 型 QT 延長症候群で torsade des pointes を誘発
	ドバミン	イノバン等	2 ~ 10 $\gamma$ , 持続静注	$\geq 5 \gamma$ で昇圧作用. 1 型 QT 延長症候群で torsade des pointes を誘発
	イソプロテレノール	プロタノール	0.01 ~ 0.03 $\gamma$ 持続静注	心拍数が 50 以上になるように量を増減. 薬物中毒による徐脈には禁忌

文献 3, 4 より改変



は  $1.0 \text{ mEq} \times \text{体重 (kg)}$  が基本となる。また欠乏量に関しては、水分不足量 = 健常時体重 - 現在体重、Na 不足量 =  $(140 - x) \times \text{体重} \times 0.6$ 、K 不足量 =  $(4.5 - y) \times 100$  で計算され、1日補給量は、維持量 + 欠乏量  $\times 1/3$  が基本となる。

カリウム投与には様々な投与制限があり、①シングルボラスショットは禁忌、②濃度：40 mEq/L 以下（末梢）、③速度：20 mEq/hr 以下、④投与量：100 mEq/日以下、⑤尿量：0.5 mL/kg/hr 以上が安全、⑥K 排泄障害時は高K血症に注意、⑦心電図でのモニターが必要、などの基本事項の遵守が必要である。

### 循環器用薬の使い方

高齢者救急例では、虚血性心疾患例以外でも、急性期疾患に伴いショックや心不全に陥る例は多く、循環器用薬の使い方に習熟しておく必要がある（表2）。循環器用薬では持続点滴投与を行う薬剤も多く、この場合用い

られる投与単位である  $\gamma = \mu\text{g}/\text{kg}$  体重/分にも習熟し、実際の用量、投与速度が瞬時に計算できるように習熟が求められる。

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ORIGINAL ARTICLE

# Association between hypertension status and the screening test for frailty in elderly community-dwelling Japanese

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To clarify the possible association of frailty with hypertension prevalence, treatment and blood pressure (BP) control in the elderly, we conducted a screening survey of 1091 elderly community-dwelling subjects aged  $\geq 65$  years, using data from public health check-ups and frailty was determined by a 25-item questionnaire, the Basic Checklist for Frailty (BCF). The significance of differences in the association of BCF categories or BCF items with each hypertension status was analyzed using multiple logistic regression analysis after adjusting for age, sex and possible confounding underlying chronic conditions. A total of 63% of subjects were hypertensive (BP  $\geq 140/90$  mm Hg), and of those, 85% were receiving antihypertensive treatment, and 56.0% of those receiving treatment had controlled BP ( $< 140/90$  mm Hg). BCF categories that showed an independent association with hypertension status were 'impaired walking status' and absence of 'impaired nutritional status' for prevalence of hypertension, 'impaired instrumental activity of daily living status' and 'impaired nutritional status' for untreated hypertension among hypertensives and 'impaired oral function' for BP-uncontrolled hypertension among treated hypertensives. In addition, BCF items that showed an independent association were 'inability to walk for more than 15 min without rest' and absence of 'Body mass index (BMI)  $< 18.5 \text{ kg m}^{-2}$ ' for prevalence of hypertension, 'weight loss of more than 2–3 kg in the past 6 months' for untreated hypertension, and 'difficulty eating hard food' for BP-uncontrolled hypertension. These observations indicate that assessment of these specified frailty categories and/or items may be useful for evaluating hypertension status in elderly community-dwelling subjects.

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**Keywords:** control; elderly; frailty; treatment

## INTRODUCTION

Providing high quality care to older adults with hypertension is growing in importance because of improved survival of patients with hypertension into old age and a growing older population at risk of developing hypertension.<sup>1</sup> Many large-scale intervention trials have proven the necessity of treatment of hypertension in the elderly, including isolated systolic hypertension. Meta-analyses of large-scale intervention trials for elderly hypertensive patients aged 60 years and older,<sup>2</sup> as well as for those aged 80 years and older,<sup>3</sup> have revealed significant reductions in morbidity and/or mortality of cerebro-cardiovascular disease by antihypertensive treatment. Moreover, the Hypertension in the Very Elderly Trial directly and clearly revealed a beneficial effect of antihypertensive treatment even in those aged 80 years and older.<sup>4</sup>

Trends in hypertension prevalence, treatment and control over time have been reported in US adults,<sup>5</sup> including those aged 60 and older<sup>6</sup> using data from two independent national surveys: the National Health and Nutrition Evaluation Survey (NHANES) III (1988–1994) and the current NHANES (1999–2004). The older population with

hypertension has been reported to have poorer blood pressure (BP) control than younger populations in the US.<sup>7,8</sup> The prevalence of hypertension in community-dwelling Japanese has also been reported to increase with age from 20 years through 80 years, reaching 50% and higher at 75 years of age and older in both sexes.<sup>9</sup> However, little is reported about trends in the treatment and BP-control of hypertension in elderly community-dwelling subjects in Japan.

On the other hand, hypertension is also known to be linked with frailty in the elderly, as assessed by weight loss, low activities of daily living (ADL), low instrumental ADL (IADL) and low physical activity.<sup>10,11</sup> In Japan, the public long-term care insurance system provides services to older adults who have been certified as requiring support (levels 1–2) or care (levels 1–5). Uncertified older adults with impaired health who are considered at high risk for needing support/care (frail elderly) are provided with preventive care services by municipalities.<sup>12</sup> Uncertified elderly subjects are given an annual health check-up by the local government, and frailty is examined using the Basic Checklist for Frailty (BCF), a yes-no questionnaire

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consisting of simple assessments for seven categories of frailty; impaired IADL status (five items), impaired walking status (five items), impaired nutritional status (two items), impaired oral function (three items), staying indoors (two items), impaired memory status (three items) and depressed mood (five items). However, few studies have examined the association of hypertension prevalence, treatment and BP-control with frailty in the elderly. Therefore, this study examined the relationship between hypertension status, and BCF categories or items in elderly community-dwelling subjects. We also studied whether this relationship could be explained by underlying chronic conditions.

## METHODS

### Subjects

In April 2008, the Regional Comprehensive Support Center of Uchinada-Town, Ishikawa, Japan distributed the BCF to all uncertified elderly community-dwelling subjects aged  $\geq 65$  years. The local government also provided a Public Health Center-based annual health check-up to these elderly subjects. Data were collected by the Uchinada-Town local government after depersonalizing participant data to ensure anonymity. We excluded elderly subjects who were already certified for long-term care insurance at the baseline. The study was formally approved by the Clinical Research Ethics Committee of Kanazawa Medical University.

### Baseline examinations

A self-administered questionnaire that included medical history, smoking condition (yes/no), regular alcohol drinking (yes/no) and time since the last meal<sup>13</sup> was completed at baseline. BMI,  $\text{kg m}^{-2}$  was calculated as weight divided by height squared. The blood condition was defined as fasting if blood was collected more than 8 h after the last meal. Serum levels of Cr, total cholesterol, HDL-cholesterol, triglycerides and glucose were measured using an automated spectrometer. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate, calculated by the Modification of Diet in Renal Disease equation<sup>14</sup> with coefficients modified for Japanese patients,<sup>15</sup>  $194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$  ( $\times 0.739$  if female),  $< 60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ . Diabetes mellitus was defined as a fasting blood glucose  $\geq 7.0 \text{ mmol l}^{-1}$  ( $126 \text{ mg dl}^{-1}$ ), a non-fasting glucose level  $\geq 11.1 \text{ mmol l}^{-1}$  ( $200 \text{ mg dl}^{-1}$ ), HbA1c  $\geq 6.5\%$  by a standardized method, or use of hypoglycemic agents and/or insulin.<sup>16</sup> Dyslipidemia was defined as fasting plasma total cholesterol level  $\geq 5.72 \text{ mmol l}^{-1}$  ( $220 \text{ mg dl}^{-1}$ ), triglycerides  $\geq 1.70 \text{ mmol l}^{-1}$  ( $150 \text{ mg dl}^{-1}$ ), high-density lipoprotein cholesterol  $< 1.04 \text{ mmol l}^{-1}$  ( $40 \text{ mg dl}^{-1}$ ), or use of lipid-lowering agents.<sup>17</sup>

### Hypertension status

Baseline BP was measured at least twice from the right arm of seated participants who had rested for more than 5 min, by trained observers using standard mercury sphygmomanometers. When the difference in the two measurements of systolic BP was greater than 5 mm Hg, another measurement was performed.<sup>18</sup> The mean of the last two stable measurements was used for analyses. Hypertension was defined as systolic BP  $\geq 140 \text{ mm Hg}$ , diastolic BP  $\geq 90 \text{ mm Hg}$ , or current antihypertensive drug treatment. Treatment was defined as reported current use of antihypertensive drug therapy. BP-control was defined as antihypertensive drug treatment associated with systolic BP  $< 140$  and diastolic BP  $< 90 \text{ mm Hg}$ .

### Statistical methods

For comparison of two groups, we used univariate analysis including  $\chi^2$  test (Fisher's exact test when needed) for comparing categorical variables and nonparametric Mann-Whitney *U* statistics for comparing the distributions of ordinal variables. Logistic regression analysis was used to identify frailty factors independently associated with any of prevalence of hypertension among all elderly subjects, untreated hypertension among hypertensive subjects and BP-uncontrolled hypertension among treated hypertensive subjects, after adjustment for age, sex and associated variables by univariate analysis. Common pitfalls associated with multivariate regression were avoided as described by

Concato *et al.*<sup>19</sup> Associated variables were selected from the data sets of status of smoking and alcohol intake, past history of stroke and ischemic heart disease, presence of CKD, diabetes mellitus and dyslipidemia and either the seven BCF categories (model-1) or the 25 questionnaire items (model-2), according to their univariate analysis *P*-value ( $< 0.20$ ) to avoid common pitfalls associated with multivariate regression.<sup>19</sup> Estimates for odds ratio and corresponding two-sided 95% confidence interval demonstrating statistical significance were derived from the regression model. Data were analyzed using SPSS (v. 16.0, Chicago, IL, USA). A probability of  $P < 0.05$  was taken as statistically significant.

## RESULTS

### Study population

A primary screening questionnaire survey was conducted on all 4050 uncertified elderly community-dwelling subjects, aged  $\geq 65$  years, living in a town in Ishikawa, Japan. Out of 3150 (77.8%) subjects who replied to the questionnaire, 1091 (427 men and 664 women) supplied complete information on all study variables, including the health check-up and were included in our study. The age of subjects (mean  $\pm$  s.d.) was  $73.5 \pm 6.1$  years (65–94 years). In the 1091 included individuals, the significance of differences in clinical factors was analyzed using univariate (Table 1) and multivariate (Tables 2 and 3) comparisons of hypertensives ( $n = 683$ ) and normotensives ( $n = 408$ ), untreated ( $n = 104$ ) and treated ( $n = 579$ ) hypertensives and BP-uncontrolled ( $n = 255$ ) and BP-controlled ( $n = 324$ ) treated hypertensives (Figure 1). A total of 62.6% of subjects were hypertensive, and of those, 84.8% were receiving antihypertensive drug treatment and BP was controlled in 56.0% of those undergoing treatment. Overall, 47.4% of hypertensive patients had controlled BP.

### Baseline factors and BCF categories and items

Compared with non-hypertensive elderly subjects, hypertensive subjects were older, and showed a higher prevalence of concomitant diabetes mellitus and dyslipidemia in univariate analysis (Table 1). Moreover, hypertensive subjects were less active and less thin than non-hypertensive subjects, as shown by associations with 'impaired walking status' and absence of 'impaired nutritional status' in the BCF categories, and associations with six BCF items including one IADL item, four items of 'impaired walking status' and absence of 'BMI  $< 18.5 \text{ kg m}^{-2}$ ' in univariate analysis (Table 1). Multiple logistic analysis using these BCF categories selected by univariate *P*-values  $< 0.20$  (model-1) revealed that two BCF categories, 'impaired walking status' and absence of 'impaired nutritional status', besides older age and diabetes mellitus, showed statistically significant association with prevalence of hypertension in elderly subjects (Table 2). In multiple logistic analysis using model-2 sets, two BCF items, 'inability to walk for more than 15 min without rest' and absence of 'BMI  $< 18.5 \text{ kg m}^{-2}$ ', besides older age and diabetes mellitus, showed statistically significant association with prevalence of hypertension in elderly subjects (Table 3).

In contrast to the entire hypertensive subjects, untreated hypertensive subjects were associated not only with clinical factors, namely absence of CKD or dyslipidemia and female sex, but also with one BCF category, 'impaired nutritional state' and with eight BCF items, including four out of five IADL items: 'able to stand up', 'weight loss of more than 2–3 kg in the past 6 months', 'going out more than once a week' and 'able to make a phone call', compared with treated hypertensive subjects in univariate analysis (Table 1). Logistic regression analysis using model-1 sets revealed that two BCF categories, 'impaired IADL status' and 'impaired nutritional

**Table 1** Characteristics of subjects according to hypertension, drug treatment and control of hypertension in community-dwelling elderly Japanese

	Hypertension			Treatment			Control		
	No	Yes	P	No	Yes	P	No	Yes	P
<i>Clinical background</i>	<i>n</i> =408	<i>n</i> =683		<i>n</i> =104	<i>n</i> =579		<i>n</i> =255	<i>n</i> =324	
Age (years)	72.0 (6.0)	74.4 (6.1)	<0.001	75.1 (6.0)	74.3 (6.1)	0.142	73.6 (6.0)	74.8(6.1)	0.015
Sex (% female)	58.3	62.4	0.186	71.2	60.8	0.048	63.9	58.3	0.172
Current smoker (%)	18.6	13.9	0.038	6.7	15.2	0.022	16.8	13.9	0.323
Regular alcohol drinker (%)	25.6	30.6	0.073	21.1	26.4	0.257	26.7	26.2	0.907
Systolic BP (mm Hg)	122 (12)	139(14)	<0.001	148 (10)	137 (14)	<0.001	149 (11)	127 (8)	<0.001
Diastolic BP (mm Hg)	74 (8)	79 (9)	<0.001	84 (8)	78 (9)	<0.001	83 (9)	75 (7)	<0.001
<i>Clinical findings on admission</i>									
Past history of stroke (%)	3.9	5.9	0.154	8.7	5.4	0.204	4.0	6.5	0.198
Ischemic heart disease (%)	1.8	3.4	0.135	2.9	3.5	0.745	4.0	3.1	0.545
CKD (%)	34.8	35.9	0.721	23.1	38.2	0.003	35.3	40.4	0.206
Diabetes mellitus (%)	11.0	20.4	<0.001	13.5	21.6	0.058	19.6	23.1	0.304
Dyslipidemia (%)	21.7	27.3	0.042	10.6	30.4	<0.001	26.7	33.2	0.094
<i>Category of BCF</i>									
Impaired instrumental activity of daily living (five items)	0.58 (1.05)	0.63 (1.10)	0.381	0.97 (1.55)	0.56 (0.99)	0.064	0.63 (1.06)	0.51 (0.93)	0.188
Impaired walking status (five items)	0.81 (1.18)	1.14 (1.36)	<0.001	1.37 (1.57)	1.10 (1.32)	0.179	1.13 (1.33)	1.08 (1.32)	0.741
Impaired nutritional status (two items)	0.22 (0.45)	0.17 (0.40)	0.049	0.28 (0.51)	0.15 (0.38)	0.004	0.14 (0.38)	0.16 (0.38)	0.532
Impaired oral function (three items)	0.57 (0.78)	0.61 (0.83)	0.590	0.67 (0.92)	0.60 (0.82)	0.615	0.67 (0.88)	0.54 (0.76)	0.195
Staying indoors (two items)	0.21 (0.47)	0.24 (0.49)	0.198	0.31 (0.57)	0.27 (0.47)	0.222	0.23 (0.47)	0.23 (0.48)	0.785
Impaired memory status (three items)	0.30 (0.58)	0.36 (0.67)	0.207	0.49 (0.85)	0.34 (0.63)	0.253	0.33 (0.59)	0.32 (0.66)	0.816
Depressed mood (five items)	0.77 (1.35)	0.86 (1.37)	0.210	0.95 (1.56)	0.85 (1.34)	0.994	0.86 (1.32)	0.83 (1.35)	0.814
<i>Questionnaire items of BCF</i>									
Do you go out alone using transportation? (% no)	13.0	15.8	0.203	24.0	14.3	0.013	16.5	12.7	0.193
Do you shop for daily necessities by yourself? (% no)	4.9	8.6	0.021	17.3	7.1	0.001	8.6	5.9	0.198
Do you manage your bank account on your own? (% no)	10.5	11.7	0.553	18.3	10.5	0.024	12.9	8.6	0.094
Do you visit your friends alone? (% no)	17.2	16.7	0.842	22.1	15.7	0.107	16.1	15.4	0.832
Are you consulted by your family or friends? (% no)	12.7	9.8	0.132	15.4	8.8	0.038	8.2	9.3	0.666
Do you climb the stairs without holding on to handrails or walls? (% no)	22.8	32.9	<0.001	33.7	32.8	0.867	33.3	32.4	0.814
Do you stand up without assistance? (% no)	10.5	16.4	0.007	24.0	15.0	0.022	15.7	14.5	0.693
Can you walk for more than 15 min without rest? (% no)	6.6	13.0	0.001	15.4	12.6	0.443	12.9	12.4	0.841
Have you fallen within the past year? (% yes)	15.7	16.4	0.757	19.6	15.5	0.155	16.9	14.5	0.437
Are you anxious about falls? (% yes)	25.2	35.6	<0.001	42.3	34.4	0.120	33.7	34.8	0.772
Have you lost more than 2–3 kg in weight in the past 6 months? (% yes)	10.8	11.1	0.861	18.3	9.8	0.012	9.4	10.2	0.756
BMI < 18.5 kg m <sup>-2</sup> (% yes)	11.3	5.7	0.001	8.7	5.2	0.160	4.7	5.6	0.647
Do you have difficulty eating hard food? (% yes)	20.6	22.8	0.385	24.0	22.6	0.752	27.5	18.8	0.014
Do you choke when you swallow liquid? (% yes)	16.7	19.0	0.327	18.3	19.2	0.829	19.6	18.8	0.813
Do you have problems with a dry mouth? (% yes)	19.9	19.2	0.786	25.0	18.1	0.102	18.8	17.6	0.703
Do you go out more than once a week? (% no)	5.1	4.8	0.816	8.7	4.1	0.048	3.9	4.3	0.811
Do you go out less frequently than last year? (% yes)	15.6	19.3	0.121	21.6	18.9	0.526	19.4	18.4	0.760
Are you told that you repeatedly ask the same questions? (% yes)	12.3	15.7	0.120	20.2	14.9	0.168	14.1	15.4	0.659
Do you look up telephone numbers, dial and make phone calls without help? (% no)	4.4	4.5	0.922	10.6	3.5	0.001	2.7	4.0	0.407
Do you sometimes forget the date? (% yes)	13.0	16.4	0.128	19.2	15.9	0.397	16.5	15.4	0.734
Have you felt unfulfilled with daily life (in the last two weeks)? (% yes)	11.8	12.0	0.905	16.3	11.2	0.139	12.5	10.2	0.371
Have you not enjoyed your life as much as you used to (in the last 2 weeks)? (% no)	8.4	9.5	0.518	11.5	9.2	0.445	8.6	9.6	0.697
Do you feel more bothered about daily matters than you did before (in the last 2 weeks)? (% yes)	20.3	25.2	0.068	25.0	25.2	0.963	25.1	25.3	0.954
Have you felt that you are not useful (in the last 2 weeks)? (% no)	15.7	15.7	0.979	16.3	15.5	0.836	16.5	14.8	0.585
Have you felt tired for no reason (in the last 2 weeks)? (% yes)	21.4	23.9	0.344	26.0	23.5	0.586	23.5	23.5	0.984

Abbreviations: BP, blood pressure; BCF: basic checklist for frailty; CKD, chronic kidney disease. Results for continuous variables are expressed as mean  $\pm$  s.d. and compared using Mann-Whitney U analysis. Discrete variables are reported as percentages and compared by  $\chi^2$ -analysis.

status, besides absence of CKD or dyslipidemia, showed a statistically significant association with untreated hypertension in elderly hypertensive subjects (Table 2). In addition, logistic regression analysis using model-2 sets revealed that 'weight loss of more than 2–3 kg in the past 6 months' among these BCF items, besides

absence of CKD or dyslipidemia, showed statistically significant association with untreated hypertension in elderly hypertensive subjects (Table 3).

Among treated hypertensive subjects, hypertensive subjects with uncontrolled BP (>140/90 mm Hg) showed a similar profile of

factors in baseline examinations and in BCF categories and items, except one BCF item, 'difficulty eating hard food', compared with hypertensive subjects with controlled BP in univariate analysis (Table 1). Logistic regression analyses revealed that 'impaired oral function' among the BCF categories in model-1 analysis (Table 2) and 'difficulty eating hard food' among the BCF items in model-2 analysis (Table 3) showed a statistically significant association with untreated hypertension in elderly community-dwelling subjects.

## DISCUSSION

The present study newly disclosed an emerging profile of hypertension status and frailty in elderly community-dwelling subjects based on data from a Public Health Center survey and Regional Comprehensive Support Center in a town in Japan. The prevalence of hypertension (62.6%) in the present study in elderly community-

**Table 2 Results of BCF categories and clinical factors by multiple logistic analysis**

	Wald	OR	95%CI	P
<i>For hypertension among all subjects</i>				
Age (years)	20.626	1.061	1.034–1.088	<0.001
Diabetes mellitus	10.048	1.862	1.268–2.736	0.002
Impaired nutritional status (two items)	8.300	0.645	0.479–0.869	0.003
Ischemic heart disease	3.332	2.288	0.940–5.568	0.068
Impaired walking status (five items)	3.269	1.107	0.991–1.236	0.070
Regular alcohol drinker	2.367	1.303	0.930–1.825	0.123
Dyslipidemia	2.296	1.272	0.931–1.737	0.129
Past history of stroke	1.499	1.473	0.792–2.740	0.220
Female sex	1.464	1.221	0.883–1.689	0.226
Current smoker	0.111	1.070	0.718–1.593	0.739
<i>For treatment among hypertensive subjects</i>				
Dyslipidemia	17.829	0.235	0.120–0.461	<0.001
CKD	9.754	0.438	0.261–0.735	0.002
Impaired IADL status (five items)	8.674	1.331	1.100–1.610	0.003
Impaired nutritional status (two items)	6.794	1.868	1.167–2.988	0.009
Current smoker	3.167	0.441	0.179–1.086	0.075
Diabetes mellitus	3.018	0.568	0.300–1.075	0.082
Female sex	2.239	1.534	0.875–2.689	0.134
Past history of stroke	1.499	1.677	0.733–3.836	0.220
Impaired walking status (five items)	0.080	0.974	0.813–1.166	0.776
Age (years)	0.042	1.004	0.963–1.047	0.836
<i>For BP-control among treated hypertensive subjects</i>				
Impaired oral function (three items)	3.957	1.236	1.003–1.523	0.047
Age (years)	3.790	0.968	0.933–1.001	0.053
Impaired IADL status (five items)	3.189	1.169	0.984–1.389	0.074
Dyslipidemia	3.036	0.712	0.486–1.043	0.081
Female sex	2.598	1.413	0.927–2.153	0.106
Past history of stroke	1.560	0.604	0.274–1.331	0.211

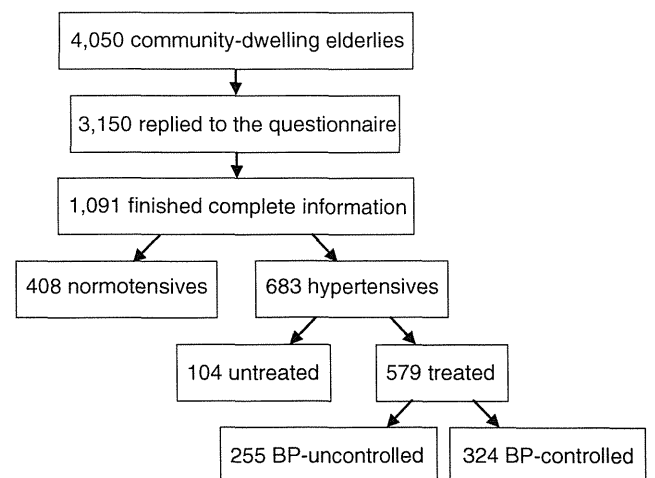
Abbreviations: BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; IADL, instrumental activity of daily living; OR, odds ratio. Adjusted by age, sex and variables selected according to their univariate analysis *P*-value (*P*<0.20).

dwelling Japanese subjects aged 65 years and older was comparable to the result (67%) in those aged 60 years and older in NHANES 1999–2004 in the US<sup>6</sup> and to that (≥50%) in those aged 75 years and older in Japan.<sup>9</sup> On the other hand, the rate of untreated hypertension in the present study, 15.2% of elderly hypertensive subjects aged 65 years and older, was rather low compared with the results in the US; 33% of those aged 60 years and older in NHANES 1999–2004<sup>6</sup> and 52% of those ≥18 years of age (mean age 58–60

**Table 3 Results of BCF items and clinical factors by multiple logistic analysis**

	Wald	OR	95%CI	P
<i>For hypertension among all subjects</i>				
Age (years)	23.338	1.067	1.039–1.096	<0.001
BMI <18.5 kg m <sup>-2</sup>	14.355	0.392	0.242–0.637	<0.001
Diabetes mellitus	9.821	1.863	1.262–2.749	0.002
Able to walk for more than 15 min (no)	4.345	1.732	1.033–2.904	0.037
Consulted by family or friends (no)	3.251	0.655	0.414–1.037	0.071
<i>For treatment among hypertensive subjects</i>				
Dyslipidemia	18.017	0.222	0.111–0.445	<0.001
CKD	9.699	0.434	0.257–0.734	0.002
Losing more than 2–3 kg in weight	7.546	2.518	1.302–4.868	0.006
Diabetes mellitus	3.802	0.526	0.275–1.003	0.051
Current smoking	2.889	0.450	0.179–1.130	0.089
Female sex	2.749	1.641	0.913–2.948	0.097
<i>For BP-control among treated hypertensive subjects</i>				
Difficulty eating hard food	6.283	1.690	1.121–2.548	0.012
Age (years)	3.683	0.968	0.938–1.001	0.055
Female sex	2.897	1.444	0.945–2.207	0.089
Able to manage bank account (no)	3.051	1.695	0.937–3.067	0.080

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio. Adjusted by age, sex and variables selected according to their univariate analysis *P*-value (*P*<0.20). BCF items and clinical factors with multiple logistic analysis *P*-values ≥0.1 are not shown.



**Figure 1** Study profile. Number of subjects per group shown for each status of hypertension.

years) in NHANES 1988–2008.<sup>5</sup> Moreover, the rate of BP-uncontrolled hypertension in the present study, 44% of treated hypertensive subjects aged 65 years and older, was also low compared with that in the US; 57% of those aged 60 years and older<sup>6</sup> and 53–73% of those  $\geq 18$  years of age.<sup>5</sup> These differences may be reflected by the major fall of BP level recently achieved in community-dwelling subjects in Japan.<sup>20</sup>

Clinical factors independently associated with the prevalence of hypertension and with untreated hypertension in the present study were similar to those previously reported in community-dwelling subjects in the US, namely older age<sup>6</sup> and presence of diabetes mellitus<sup>6</sup> for prevalence of hypertension and absence of CKD<sup>5,6</sup> and absence of dyslipidemia<sup>5</sup> for untreated hypertension.

Logistic regression analysis in the present study also revealed that specified BCF categories and/or items were independently associated with hypertension status. First, two BCF categories, ‘impaired walking status’ and absence of ‘impaired nutritional status’, besides presence of diabetes mellitus, were independently associated with prevalence of hypertension in elderly subjects in logistic analysis using model-1 data sets. In addition, two BCF items, ‘inability to walk for more than 15 min without a rest’ and absence of ‘BMI  $< 18.5 \text{ kg m}^{-2}$ ’, were further shown to have an independent association with prevalence of hypertension in elderly subjects in logistic analysis using model-2 data sets. A possible explanation for the association of ‘impaired walking status’ or ‘inability to walk for more than 15 min without rest’ with prevalence of hypertension is that hypertension itself may cause physical frailty resulting in a decline in walking ability in the elderly, since elderly subjects with frailty syndrome with low physical activity had higher BP than the non-frailty group,<sup>11</sup> and since hypertension was independently associated with shorter distance on the 6-minute walk test in elderly subjects.<sup>21</sup> Another possible explanation is that daily practice of walking may prevent hypertension even in the elderly population, since subjects walking 1 hour or more per day had a lower prevalence of hypertension in a large population of frail and very old subjects living in the community.<sup>22</sup> On the other hand, the observation in the present study of the independent association of thinness (BMI  $< 18.5 \text{ kg m}^{-2}$ ) with lower prevalence of hypertension in the elderly is partly compatible with a previous report of an association of being underweight (BMI  $< 20 \text{ kg m}^{-2}$ ) with lower prevalence of hypertension in elderly subjects,<sup>23</sup> although it is well-known that BMI greater than the reference value ( $25 \text{ kg m}^{-2}$ ) is independently associated with a greater likelihood of hypertension in the elderly.<sup>6</sup>

Second, two BCF categories, ‘impaired IADL status’ and ‘impaired nutritional status’, besides absence of CKD or dyslipidemia, were independently associated with untreated hypertension in hypertensive elderly subjects. The latter finding was further supported by the independent association of ‘weight loss of more than 2–3 kg in the past 6 months’ in model-2 logistic analysis using BCF items (Table 3). Although the precise mechanism of the association of ‘impaired IADL status’ with untreated hypertension in the elderly is unknown, IADL is a well-known indicator of the ability to live independently in the community. Okamura *et al.*<sup>24</sup> reported that elderly residents with systolic hypertension ( $\geq 160 \text{ mm Hg}$ ) in two communities located in Akita and Kochi Prefectures showed a 3.41 times higher odds ratio for having low IADL scores than those with normal BP. Hayakawa *et al.*<sup>25</sup> reported a significant relationship between decrease in IADL score and cardiovascular risk factors including hypertension, dyslipidemia, diabetes mellitus and smoking, in a cohort in Japan. The present observation of an association between decline in IADL score and untreated hypertension is, at least in part, compatible with the reports

of Okamura *et al.*<sup>24</sup> and Hayakawa *et al.*<sup>25</sup> Therefore, active treatment of hypertension in elderly community-dwelling subjects may be linked to prevention of future decline in IADL in Japanese elderly, allowing them to live a healthy and active life. On the other hand, the precise mechanism of the independent association of weight loss (of more than 2–3 kg in the past 6 months) with untreated hypertension in hypertensive elderly subjects is also unknown. One of the possible explanations for this is that weight loss as opposed to weight gain may often be overlooked as a problem linked to hypertension by healthcare providers, the public and elderly subjects themselves, as BMI  $< 25 \text{ kg m}^{-2}$  compared with BMI  $\geq 25 \text{ kg m}^{-2}$  was reported to be independently associated with a greater likelihood of untreated hypertension in elderly subjects in the US.<sup>6</sup> Another possibility is that weight loss more often observed in elderly subjects with untreated hypertension might be caused by past antihypertensive drug treatment and result in cessation of drug treatment by elderly subjects themselves, as unintended weight loss in the elderly may be caused by polypharmacy through dysgeusia and anorexia due to many individual medications.<sup>26</sup>

Third, ‘impaired oral function’ in the BCF categories and ‘difficulty eating hard food’ in the BCF items were independently associated with BP-uncontrolled hypertension in treated hypertensive elderly subjects in respective logistic regression analysis models. One of the possible explanations for this is that oral dysfunction may directly cause trouble swallowing pills, resulting in underuse of antihypertensive medication in these subjects.<sup>27</sup> Another possibility is that periodontal disease may cause both ‘difficulty eating hard food’ and BP-uncontrolled hypertension. The severity of periodontal disease<sup>28,29</sup> and tooth loss due to the disease<sup>30</sup> were significantly related to hypertension independent of age, although inconsistent results were also reported in middle-aged men.<sup>31</sup> Moreover, periodontal disease is reported to contribute to poor BP control in subjects aged 70 years and older.<sup>32</sup>

In the present study, specified BCF categories and/or items were newly identified as factors independently associated with prevalence of hypertension, untreated hypertension and BP-uncontrolled hypertension in elderly community-dwelling subjects. These frailty categories and items may be useful for evaluating hypertension status in elderly community-dwelling subjects. However, in view of the single community model, care must be taken in interpreting these results, and further evaluation in multi-regional trials is needed. Frailty assessed by comprehensive geriatric assessments and a precise health examination should be included in future studies to elucidate the mechanisms of the individual associations of BCF categories/items and hypertension status. Stratified sampling of BCF scores according to the kinds of antihypertensive drugs used, including renin-angiotensin blockers, is also needed in future studies, because the renin-angiotensin system is thought to have a crucial role in aging and/or frailty.<sup>33</sup>

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## ORIGINAL ARTICLE

# Association of severe hypertension with pneumonia in elderly patients with acute ischemic stroke

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Pneumonia is one of the most frequent complications in elderly patients with acute ischemic stroke. Although severe hypertension is often observed in the early phase of acute stroke, there are few studies of acute hypertension as a factor influencing the incidence of stroke-associated pneumonia (SAP) in elderly subjects with acute ischemic stroke. To assess the association of acute phase blood-pressure elevation with the incidence of SAP, we compared 10 elderly patients with acute ischemic stroke complicated with severe hypertension ( $\geq 200/120$  mm Hg) with 43 patients with moderate hypertension (160–199/100–119 mm Hg), as well as with 65 control normotensive or mildly hypertensive ( $< 160/100$  mm Hg) controls on admission. Data were collected on known risk factors, type of ischemic stroke and underlying chronic conditions. The significance of differences in risk factors was analyzed using univariate and multivariate comparisons of 38 SAP cases and others, 8 SAP death cases and others, and 28 patients with poor outcome associated with in-hospital death or artificial feeding at discharge and others. After adjustment for potential confounding factors, the relative risk estimates for SAP, SAP death and poor outcome were 2.83 (95% confidence interval 1.14–7.05), 5.20 (1.01–26.8) and 6.84 (1.32–35.4), respectively, for severe hypertension relative to normotensive or mildly hypertensive controls. We conclude that severe hypertension on admission is an independent predictive factor for SAP in elderly patients with acute ischemic stroke.

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**Keywords:** elderly; ischemic stroke; pneumonia; severe hypertension

## INTRODUCTION

Stroke-associated pneumonia (SAP) is among the leading complications of stroke,<sup>1–11</sup> and is an important cause of death after cerebrovascular events.<sup>1,3,4</sup> SAP is most likely to develop in patients who are seriously ill and those with dysphagia. There are various data available on independent predictors of SAP in treated acute stroke patients. In those studies, a number of risk factors have been reported, such as lower baseline Glasgow Coma Scale score,<sup>4–6</sup> dysphagia,<sup>7–9</sup> male sex,<sup>3,7,9,10</sup> stroke subtype,<sup>8,9</sup> diabetes,<sup>10</sup> ischemic heart disease<sup>9</sup> and chronic congestive heart failure.<sup>11</sup> SAP is known to occur more frequently in elderly patients,<sup>2,3,9–11</sup> although conflicting results are also reported.<sup>4</sup> Besides SAP, severe arterial hypertension is another frequent medical complication observed in patients with acute ischemic stroke within the first week after admission.<sup>12–16</sup> This increased blood pressure (BP) falls spontaneously within the first week, without specific antihypertensive therapy.<sup>17</sup> Severe hypertension in the early phase of acute ischemic stroke is another sign associated with poor functional outcome and higher mortality.<sup>18–20</sup> As yet, however, there are only limited data on the association of SAP with severe arterial hypertension in patients with acute stroke. We here present a study of SAP in elderly patients admitted to our hospital with acute ischemic stroke associated with severe hypertension

with systolic BP (SBP)  $\geq 200$  mm Hg and/or diastolic BP (DBP)  $\geq 120$  mm Hg on admission.<sup>21</sup> The results were compared with those in elderly patients with acute ischemic stroke with moderate hypertension with SBP 160–199 mm Hg and/or DBP 100–119 mm Hg, who may develop signs of encephalopathy,<sup>22</sup> and with normotensive and/or mildly hypertensive controls with SBP  $< 160$  mm Hg and DBP  $< 100$  mm Hg.

## METHODS

### Subjects

Consecutive patients admitted to the Geriatric Emergency Ward of Kanazawa Medical University Hospital, a major urban hospital in Ishikawa Prefecture, Japan, with a diagnosis of ischemic stroke during 2002–2010 were recruited into the study. Patients participating in this study were 70 years of age or older, and had both clinical and neuroimaging evidence of ischemic cerebral infarction. Only patients with symptom onset within 24 h of admission were included in this study. All subjects were systematically evaluated. Neurovascular evaluation, including assessment of underlying chronic conditions, serial neurological examinations including Glasgow Coma Scale, 12-lead electrocardiograms, chest X-ray examination and transthoracic echocardiograms, in addition to routine hematologic and chemistry tests were completed in all subjects. The presence of dysphagia was screened in all the study subjects. For this, clinical examination and a water swallowing test with pulse oximetry were



performed, and a drop in arterial oxygen saturation of >2% within 2 min after swallowing was considered clinically significant to detect dysphagia with silent aspiration or cough.<sup>23</sup> Dysphagia with impaired voice or complete dysphagia without swallowing was also considered to indicate the presence of dysphagia. During this period, vital signs, including noninvasive cuff BP, pulse rate and body temperature, were measured at least every 2 h during the first 24 h and continued every 2–8 h up to 72 h. Antihypertensive medication was given at the discretion of physicians not involved in the study, who in general followed the recommendations of the Guidelines for the Management of Hypertension published in 2009 by the Japanese Society of Hypertension Committee (JSH 2009)<sup>24</sup> for BP of 220/120 mm Hg and higher. The patients were divided into three groups according to the record of the highest mean SBP and/or DBP of two measurements every 2 h during the first 24 h after admission; control patients with normotension to mild hypertension (SBP <160 mm Hg and DBP <100 mm Hg), patients with moderate hypertension (SBP 160–199 mm Hg and/or DBP 100–119 mm Hg) and those with severe hypertension (SBP ≥200 mm Hg and/or DBP ≥120 mm Hg).

### Assessment of brain lesions

All patients underwent brain magnetic resonance imaging and magnetic resonance angiography on the first day of admission. Imaging was performed using a 1.5-T MRI (Model: MAGNETOM Avanto, Siemens Medical Solution, Erlangen, Germany). Acute ischemic lesions were assessed by diffusion-weighted imaging with apparent diffusion coefficient. Ischemic lesions on diffusion-weighted imaging were classified as single lesions (corticosubcortical lesion, cortical lesion, subcortical lesion with diameter >15 mm or subcortical lesion with diameter <15 mm), scattered lesions in one vascular territory (small (<15 mm) scattered lesions or confluent (>15 mm) lesions with an additional lesion) and multiple lesions in multiple vascular territories (in the unilateral anterior circulation, posterior circulation, bilateral anterior circulation or anterior and posterior circulation). Stroke subtype classification was performed according to a previous report.<sup>25</sup> Patients with diffusion-weighted imaging findings of a corticosubcortical single lesion and those with multiple lesions in both the anterior and posterior circulation were classified as having cardiac embolism if they had atrial fibrillation and/or another cardioembolic source. Those with subcortical small lesion(s) (<15 mm) were classified as having small-vessel occlusion. Those with subcortical lesion(s) (<20 mm) were also classified as having small-vessel occlusion according to the recommendations in the report.<sup>25</sup> Other patients with atrial fibrillation and/or another cardioembolic source were classified as having cardiac embolism. Patients without a cardioembolic source were classified as having large-artery atherosclerosis. Patients with transient ischemia with no visible lesion on diffusion-weighted imaging were excluded from this study.

### Underlying chronic conditions

We observed the clinical features of the enrolled patients, including past history of stroke, ischemic heart disease, chronic congestive heart failure, chronic kidney disease, diabetes mellitus and hypertension under treatment with an antihypertensive agents. Operational definitions of each preexisting chronic condition were established prior to data collection, including past history of stroke (evidence of chronic phase of stroke on magnetic resonance imaging), ischemic heart disease (evidence on electrocardiography or echocardiography), chronic congestive heart failure (left ventricular ejection fraction ≤40%), chronic kidney disease (estimated glomerular filtration rate with coefficients modified for Japanese patients:<sup>26</sup>  $194 \times Cr^{-1.094} \times age^{-0.287}$  ( $\times 0.739$  if female)  $<60 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ ), diabetes mellitus (use of hypoglycemic agents and/or insulin) and hypertension (use of antihypertensive agents).

### Definitions of SAP and poor outcome

Patients with (without) SAP are referred to as SAP+ (SAP-) patients. The definition of SAP includes either the clinical finding of rales or dullness to percussion and one of the following: purulent sputum, isolation of the organism, chest radiograph showing evidence of an infiltrate/consolidation/cavitation or pleural effusion, and one of the following: purulent sputum, isolation of the agent or antibody evidence of an agent.<sup>7</sup> Definition of SAP death was defined as death in SAP patients during in-hospital treatment. The

definition of poor outcome was either in-hospital death or artificial feeding at discharge. Patients who had a prior history of dysphagia before the index stroke and those who required mechanical ventilation during the hospital stay were excluded. Patients who had another identifiable source of infection before the development of pneumonia and those who had fever before stroke onset were also excluded.

### Statistical methods

For comparing cases and controls, we used univariate analyses including  $\chi^2$  test (Fisher's exact test when needed) for comparing categorical variables and nonparametric Mann-Whitney *U* statistics for comparing the distributions of ordinal variables. Continuous variables were compared among the three hypertensive states by one-way ANOVA, with Tukey's test for *post-hoc* comparisons. The distribution of serum C-reactive protein level was positively skewed, and was therefore log transformed before statistical comparison. Results were then expressed in natural units for ease of interpretation. Discrete variables were reported as percentages and compared by  $\chi^2$  analysis. Logistic regression analysis was used to identify factors independently associated with SAP after adjustment for confounding variables. Common pitfalls associated with multivariate regression were avoided as described by Cibciti *et al.*<sup>27</sup> The odds ratio (OR) for severe hypertension associated with various conditions was calculated by logistic regression analysis, adjusting for age, sex and all associated variables selected according to their univariate analysis *P*-value ( $P < 0.10$ ). Estimates for OR and corresponding two-sided 95% confidence interval (CI) demonstrating statistical significance were derived from the regression model. Data were analyzed using SPSS (v. 16.0, Chicago, IL, USA). A probability of  $P < 0.05$  was taken as statistically significant.

## RESULTS

### Study population

A total of 118 patients (mean age  $84.6 \pm 5.4$  years, range 72–96 years; 58 men,  $85.0 \pm 5.1$  years; 60 women,  $84.2 \pm 5.7$  years) with complete ischemic stroke were included. The mean duration of treatment was  $25.7 \pm 7.2$  days (range 1–109 days). Hemispheric infarction was documented in 104 (88%) patients, with more than one hemispheric territory affected in 14 of them. According to the results of magnetic resonance imaging, 62 patients were classified as having large-artery atherosclerosis, 22 small-vessel occlusion and 34 cardiac embolism.

### Characteristics of SAP

SAP occurred in 38 (30.5%) out of 118 patients, with a mean latency from admission of  $1.8 \pm 2.7$  days (range 0–12 days). These 38 SAP+ patients were compared with 80 SAP- patients (Table 1). SAP+ patients had higher mean SBP compared with SAP- patients ( $166 \pm 31$  vs.  $150 \pm 28$  mm Hg,  $P=0.006$ ), higher mean pulse BP ( $80 \pm 22$  vs.  $69 \pm 20$  mm Hg,  $P=0.018$ ), lower Glasgow Coma Scale score ( $11.8 \pm 3.4$  vs.  $13.6 \pm 2.6$ ,  $P=0.001$ ), higher WBC count ( $8.13 \pm 2.55$  vs.  $6.08 \pm 1.42 \times 10^{12} \text{ l}^{-1}$ ,  $P < 0.001$ ), higher serum C-reactive protein (7.9 with s.d. range 1.5–40.9 vs. 3.8 with s.d. range 1.0–6.0,  $P < 0.001$ ) and higher incidence of dysphagia (44.7% vs. 15.0%,  $P=0.001$ ) on admission. However, there was no significant difference in age, sex, type of ischemic stroke or underlying chronic conditions including prior use of antihypertensive agents (Table 1).

### Clinical predictors of SAP

The Glasgow Coma Scale score was significantly higher in both the moderate hypertensive group and severe hypertensive group than in the control group. WBC count was also significantly higher in the severe hypertensive group, and the incidence of dysphagia was significantly higher in the moderately hypertensive group than in the control group. The clinical background, frequency of underlying chronic conditions and previous use of antihypertensive medication were similar in the three hypertensive states, although previous use of

**Table 1 Characteristics of SAP+ and SAP- patients**

	SAP+ n=38	SAP- n=80	P-value
<i>Clinical background</i>			
Age (years)	84.9 ± 5.8	84.4 ± 5.2	0.518
Male: female	22:16	36:44	0.238
<i>Type of ischemic stroke</i>			
Large-artery atherosclerosis: n (%)	17 (44.7)	45 (56.3)	0.324
Small-vessel occlusion: n (%)	7 (18.4)	15 (18.8)	0.955
Cardiac embolism: n (%)	14 (36.8)	20 (25.0)	0.198
<i>Clinical findings on admission</i>			
BMI (kg m <sup>-2</sup> )	19.4 ± 3.0	20.0 ± 3.2	0.677
SBP (mm Hg)	166 ± 31	150 ± 28	0.006
DBP (mm Hg)	87 ± 17	81 ± 19	0.066
Pulse pressure (mm Hg)	80 ± 22	69 ± 20	0.018
Glasgow Coma Scale	11.8 ± 3.4	13.6 ± 2.6	0.001
WBC count (×10 <sup>12</sup> l <sup>-1</sup> )	8.13 ± 2.55	6.08 ± 1.42	<0.001
Serum C-reactive protein (mg l <sup>-1</sup> )	7.9 (1.5–40.9)	3.8 (1.0–6.0)	<0.001
Serum albumin (g l <sup>-1</sup> )	34.8 ± 4.1	35.7 ± 4.5	0.189
Dysphagia (%)	44.7	15.0	0.001
<i>Underlying chronic conditions</i>			
Past history of stroke (%)	34.2	40.0	0.547
Ischemic heart disease (%)	10.5	10.0	0.930
Congestive heart failure (%)	26.3	16.3	0.199
Chronic kidney disease (%)	7.9	8.8	0.877
Diabetes mellitus (%)	23.7	16.3	0.335
Hypertension treatment (%)	26.3	23.8	0.763
ARB alone (%)	5.3	2.5	0.440
ACEI alone (%)	2.6	0	0.147
CaB alone (%)	5.3	8.8	0.507
Thiazide alone (%)	0	1.3	0.491
Two or more antihypertensives (%)	13.2	11.3	0.766
ARB with/without others (%)	13.2	10.0	0.610
ACEI with/without others (%)	7.9	2.5	0.176
CaB with/without others (%)	7.9	16.3	0.217
Thiazide with/without others (%)	10.5	5.0	0.267

Abbreviations: ACEI, angiotensin I-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker; CaB, dihydropyridine calcium-channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Results for continuous variables are expressed as mean ± s.d. and compared using Mann-Whitney *U* analysis. Discrete variables are reported as percentages and compared by  $\chi^2$  analysis.

antihypertensive medication in moderately hypertensives was significantly higher than that in normotensive/mildly hypertensive controls (Table 2).

Logistic regression analysis using age, sex, Glasgow Coma Scale score, WBC count, log(serum C-reactive protein), dysphagia and hypertensive state as confounding factors revealed that log(serum C-reactive protein) (OR: 1.89, 95% CI: 1.26–2.85,  $P=0.002$ ), WBC count (OR: 1.47, 95% CI: 1.11–1.95,  $P=0.008$ ) and hypertensive state (OR: 2.27, 95% CI: 1.04–4.97,  $P=0.040$ ) were independently and significantly associated with an increased risk of SAP. Conditional logistic regression analysis revealed a significantly higher risk of SAP in those with severe hypertension, with adjusted OR estimate of 2.83 and CI 1.14–7.05, with control BP level as the reference group (Table 3). Even when the previous use of antihypertensive medication was added as another confounding factor to those above, hypertensive state was

still independently and significantly associated with an increased risk of SAP (OR: 2.26, 95% CI: 1.03–4.94,  $P=0.041$ ) by logistic regression analysis, and a significant increase in the risk of SAP in those with severe hypertension (OR: 2.85, 95% CI: 1.13–7.16,  $P=0.026$ ) was still revealed with control BP level as the reference group by conditional logistic regression analysis.

#### SAP death and poor outcome

On the other hand, out of the eight patients with SAP death, three patients showed severe hypertension, three moderate hypertension and two control BP levels. Logistic regression analysis using age, sex, Glasgow Coma Scale score, WBC count, log(serum C-reactive protein), dysphagia and hypertensive state as confounding factors revealed that male sex (OR: 23.0, 95% CI: 1.66–319,  $P=0.019$ ) and hypertensive state (OR: 5.69, 95% CI: 1.24–26.1,  $P=0.025$ ) were independently and significantly associated with an increased risk of SAP death. Conditional logistic regression analysis adjusted by the same confounding factors revealed a significant increase in the risk of SAP death in those with severe hypertension on admission, with an adjusted OR estimate of 5.20 and CI 1.01–26.8, with control BP level as the reference group (Table 4). Even when the previous use of antihypertensive medication was added as another confounding factor to the above, hypertensive state was still independently and significantly associated with an increase risk of SAP death (OR: 5.92, 95% CI: 1.25–28.1,  $P=0.025$ ) by logistic regression analysis, although a tendency for increased risk of SAP death in those with severe hypertension (OR: 6.11, 95% CI: 0.84–44.6,  $P=0.074$ ) was still revealed with control BP level as the reference group by conditional logistic regression analysis.

Besides the 8 patients with SAP death, 3 patients died from other causes in hospital and 17 patients were receiving artificial feeding at discharge. Logistic regression analysis using the same confounding factors revealed that dysphagia (OR: 65.2, 95% CI: 9.74–437,  $P<0.001$ ) and hypertensive state (OR: 5.66, 95% CI: 1.32–24.3,  $P=0.020$ ) were independently and significantly associated with an increased risk of poor outcome associated with in-hospital mortality and artificial feeding at discharge. Conditional logistic regression analysis adjusted by the same confounding factors revealed a significant increase in the risk of poor outcome in those with severe hypertension on admission, with adjusted OR estimate of 6.84 and CI 1.32–35.4, with control BP level as the reference group (Table 5). Even when the previous use of antihypertensive medication was added as another confounding factor to those above, hypertensive state was still independently and significantly associated with an increased risk of poor outcome (OR: 7.43, 95% CI: 1.24–44.6,  $P=0.028$ ) by logistic regression analysis, and a significant increase in the risk of poor outcome in those with severe hypertension (OR: 9.78, 95% CI: 1.24–77.4,  $P=0.031$ ) was still revealed with control BP level as the reference group by conditional logistic regression analysis.

#### DISCUSSION

In this study, we attempted to compare SAP+ patients with SAP- patients in the acute phase of ischemic stroke and obtain evidence of predictors of SAP in elderly patients with a mean age of 84.6 years. Because older age is one of the risk factors for SAP,<sup>2,3,9–11</sup> our study was carried out in one of the most susceptible groups for SAP. Besides age, we adopted known risk factors for SAP as possible confounding factors in the present study, such as sex<sup>3,7,9,10</sup>, Glasgow Coma Scale score,<sup>4–6</sup> dysphagia,<sup>7–9</sup> stroke subtype,<sup>8,9</sup> diabetes,<sup>10</sup> ischemic heart disease<sup>9</sup> and chronic congestive heart failure.<sup>11</sup> We also adopted chronic kidney disease as a factor, because the risk of hospitalization

**Table 2** Characteristics of controls, moderate and severe hypertensives

	Controls n=65	Moderate hypertensives n=43	Severe hypertensives n=10	P-value
<i>Clinical background</i>				
Age (years)	84.2 ± 5.8	85.5 ± 4.8	83.5 ± 5.2	0.356
Male: female	36: 29	18: 25	4: 6	0.329
<i>Type of ischemic stroke</i>				
Large-artery atherosclerosis: n (%)	34 (52.3)	24 (55.8)	4 (40.0)	0.671
Small-vessel occlusion: n (%)	13 (20.0)	17 (16.3)	2 (20.0)	0.885
Cardiac embolism: n (%)	18 (27.7)	12 (27.9)	4 (40.0)	0.722
<i>Clinical findings on admission</i>				
BMI (kg m <sup>-2</sup> )	19.9 ± 3.1	20.0 ± 3.2	18.1 ± 3.4	0.625
SBP (mm Hg)	133.5 ± 18.4	175.0 ± 9.3***	210.3 ± 13.9*****	<0.001
DBP (mm Hg)	73.9 ± 14.6	90.6 ± 14.9***	106.7 ± 17.7*****	<0.001
Pulse pressure (mm Hg)	60.5 ± 15.2	83.8 ± 16.5***	103.4 ± 12.1*****	<0.001
Glasgow Coma Scale	13.9 ± 3.6	11.9 ± 3.6**	12.2 ± 2.3**	0.002
WBC (×10 <sup>12</sup> l <sup>-1</sup> )	6.47 ± 1.81	6.72 ± 2.18	8.59 ± 2.59***	0.010
Serum C-reactive protein (mg l <sup>-1</sup> )	3.6 (0.8–15.1)	3.1 (1.0–10.2)	5.5 (1.9–15.8)	0.471
Serum albumin (g l <sup>-1</sup> )	35.4 ± 4.5	35.2 ± 3.9	36.3 ± 6.2	0.784
Dysphagia (%)	13.6	39.5**	30.0	0.009
<i>Underlying chronic conditions</i>				
Past history of stroke (%)	40.0	32.6	50.0	0.540
Ischemic heart disease (%)	6.2	14.0	20.0	0.242
Congestive heart failure (%)	16.9	20.9	30.0	0.603
Chronic kidney disease (%)	6.2	9.3	20.0 <sup>#</sup>	0.339
Diabetes mellitus (%)	15.5	20.9	30.0	0.490
Hypertension treatment (%)	18.5	34.9*	20.0	0.146
ARB alone (%)	3.1	2.3	10.0	0.479
ACEI alone (%)	0	2.3	0	0.422
CaB alone (%)	4.6	11.6	10.0	0.394
Thiazide alone (%)	0	2.3	0	0.422
Two or more antihypertensives (%)	10.8	16.3	0	0.335
ARB with/without others (%)	10.8	14.0	0	0.452
ACEI with/without others (%)	1.5	7.0	10.0	0.254
CAB with/without others (%)	9.2	20.9	10.0	0.212
Thiazide with/without others (%)	6.2	9.3	0	0.555
SAP+ (%)	21.5	39.5 <sup>#</sup>	70.0**	0.004
SAP death (%)	3.1	7.0	30.0* <sup>1</sup>	0.007

Abbreviations: ACEI, angiotensin I-converting enzyme inhibitor; ARB, angiotensin II-receptor blocker; CaB, dihydropyridine calcium-channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Results for continuous variables are expressed as mean (95% CI) (range) and compared using one-way ANOVA with Tukey's *post-hoc* analysis. Discrete variables are reported as percentages and compared by  $\chi^2$  analysis. Keys as in Table 1. <sup>#</sup>*P*<0.10, \**P*<0.05, \*\**P*<0.01 and \*\*\**P*<0.001 vs. controls. <sup>1</sup>*P*<0.10, \**P*<0.05, \*\**P*<0.01 and \*\*\**P*<0.001 vs. moderate hypertensives.

due to pneumonia is also greater in these patients.<sup>28</sup> Indeed, univariate analysis revealed that elderly SAP+ patients had a significantly lower mean Glasgow Coma Scale score and a higher incidence of dysphagia, as well as higher WBC count and log(serum C-reactive protein) on admission, compared with SAP- patients.

In the present study, however, the most notable finding was the significant association of severe hypertension, defined as 200/120 mm Hg or higher, on admission with the occurrence of SAP. Univariate analysis revealed that elderly SAP+ patients had significantly higher SBP and pulse pressure on admission compared with SAP- patients (Table 1). There were significant differences in Glasgow Coma Scale score, WBC count and incidence of dysphagia among the three BP groups (Table 2). However, even after adjustment for these known confounding factors, severe hypertension on admission was

significantly and independently associated with SAP, with OR 2.83 and CI 1.14–7.05, with control BP level as the reference group (Table 3).

The precise mechanism of this association is not known. SAP is most likely to develop in patients who are seriously ill, and aspiration due to dysphagia may be one of the most important causes of this complication. Hypertension in the elderly is a well-known risk factor for silent cerebral infarction, which is a predictor of not only overt stroke<sup>29</sup> but also aspiration pneumonia due to dysphagia.<sup>29,30</sup> On the other hand, known hypertension before stroke was significantly associated with elevated post-stroke BP.<sup>15</sup> In the present study, the incidence of both dysphagia and known hypertension under treatment with antihypertensive agents was significantly higher in patients with moderate hypertension on admission compared with normotensive and/or mildly hypertensive controls (Table 2). Although patients with

**Table 3 Association of SAP with hypertensive state on admission after adjustment for potential confounders**

Hypertensive state	Number of cases	Relative risk estimate (95% CI) <sup>a</sup>	P-value
Controls <sup>b</sup>	14	1.0	
Moderate hypertensives	17	2.36 (0.76–7.29)	0.136
Severe hypertensives	7	2.83 (1.14–7.05)	0.025

Abbreviation: CI, confidence interval.

<sup>a</sup>Adjusted for age, sex, Glasgow Coma Scale score, WBC, log(serum C-reactive protein) and dysphagia.<sup>b</sup>Reference group.**Table 4 Association of SAP death with hypertensive state on admission after adjustment for potential confounders**

Hypertensive state	Number of cases	Relative risk estimate (95% CI) <sup>a</sup>	P-value
Controls <sup>b</sup>	2	1.0	
Moderate hypertensives	3	2.57 (0.24–27.3)	0.434
Severe hypertensives	3	5.20 (1.01–26.8)	0.049

Abbreviation: CI, confidence interval.

<sup>a</sup>Adjusted for age, sex, Glasgow Coma Scale score, WBC, log(serum C-reactive protein) and dysphagia.<sup>b</sup>Reference group.**Table 5 Association of poor outcome (in-hospital death or artificial feeding at discharge) with hypertensive state on admission after adjustment for potential confounders**

Hypertensive state	Number of cases	Relative risk estimate (95% CI) <sup>a</sup>	P-value
Controls <sup>b</sup>	9	1.0	
Moderate hypertensives	14	2.06 (0.26–16.3)	0.491
Severe hypertensives	5	6.84 (1.32–35.4)	0.022

Abbreviation: CI, confidence interval.

<sup>a</sup>Adjusted for age, sex, Glasgow Coma Scale score, white blood cell count, log(serum C-reactive protein) and dysphagia.<sup>b</sup>Reference group.

a prior history of dysphagia before the index stroke were excluded in the present study, these observations may indicate that known hypertension would influence subclinical swallowing dysfunction through hypertension-induced brain damage such as silent cerebral infarction before overt ischemic stroke. However, there was no significant difference in the incidence of dysphagia and known hypertension between patients with severe hypertension on admission and patients with control BP. Moreover, conditional logistic regression analysis revealed a significant increase in the risk of SAP in those with severe hypertension compared with control BP patients, even after adjustment for dysphagia (Table 3) and known hypertension under antihypertensive treatment as confounding factors.

Another potential confounder may be drug therapy. ACEI may decrease the prevalence of aspiration pneumonia in elderly subjects, probably due to stimulation of the cough reflex.<sup>31,32</sup> Moreover, several other antihypertensive agents are reported to modify the risk of community-acquired pneumonia.<sup>33</sup> In the present study, the rate of

antihypertensive treatment prior to ischemic stroke was significantly higher in the moderate hypertension group than in the control group. However, there was no significant difference in the rate of single or combination use of particular antihypertensive agents between the severe hypertensive group and either the control group or moderate hypertensive group. Moreover, there was no significant difference in the rate of single or combined use of particular antihypertensive agents between SAP+ and SAP– patients. These results indicate that the effect(s) of any antihypertensive treatment prior to ischemic stroke on SAP is minimal.

Another possible explanation may be overactivation of the sympathetic nervous system. Acute severe hypertension in the early phase of acute ischemic stroke is related to stroke-induced changes in sympathoadrenergic activity.<sup>12,15,34</sup> Dysphagia and subsequent aspiration are considered to account for the high incidence of bacterial pneumonia after stroke. However, aspiration alone cannot explain the high incidence of SAP,<sup>35</sup> because aspiration occurs in healthy adults during sleep without inducing pneumonia.<sup>36</sup> The high incidence of pneumonia in patients with acute ischemic stroke may be due to stroke-induced immunodeficiency primarily caused by overactivation of the sympathetic nervous system, which was described in mouse models of cerebral ischemia.<sup>37,38</sup> In these animal models, experimental stroke propagated bacterial aspiration ranging from harmless intranasal colonization to harmful pneumonia, which was exacerbated by immunodepression due to sympathetic hyperactivity. Moreover, immediately after admission, chest X-ray infiltrate was noted only in 4 normotensive and/or mildly hypertensive control subjects, but not in the 7 subjects with severe hypertension on admission, out of the 38 SAP patients in the present study (data not shown). This evidence may suggest that severe hypertension preceded SAP, at least in the seven patients, in our study. Although we did not determine sympathetic activity including circulating levels of catecholamines in the present study, overactivation of the sympathetic nervous system could induce both severe hypertension and immunodepression, resulting in SAP in our elderly ischemic stroke patients. Further, studies are required to elucidate the precise mechanism of the association of severe hypertension with SAP.

In the present study, severe hypertension on admission was an independent predictor not only of SAP but also of SAP death (Table 4), and of poor outcome associated with in-hospital mortality and artificial feeding at discharge (Table 5). Severe hypertension in the early phase of acute ischemic stroke is a predictor of a poor outcome, with higher mortality and a poor functional outcome.<sup>18–20</sup> Because SAP is an important cause of death<sup>1,3,4</sup> and a worse long-term clinical outcome,<sup>4</sup> the association of severe hypertension with poor outcome would, at least in part, be explained by higher SAP death and poor functional outcome in those with severe hypertension revealed in the present study. However, in view of the small sample size, care must be taken when these results are interpreted and further evaluation in larger trials is needed. Moreover, four patients suffered from SAP already on admission, but remaining 34 patients with SAP were diagnosed as nosocomial, hospital-acquired pneumonia occurring during hospitalization. Microbiological examination of tracheal specimens and/or blood cultures did not detect atypical pathogens, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* or *Legionella pneumophila* (data not shown), suggesting aspiration pneumonia as predominant type in these 38 SAP patients. However, we previously reported association between human metapneumovirus seroprevalence and hypertension in elderly subjects.<sup>39</sup> Further, studies including examination of pathogen(s) are also needed to elucidate precise mechanism for the association of severe hypertension and SAP.