表8　Zarit Careburden Scale の比較

	明らかな大脳白質病変を有さない群（PVH grade 0, 1）	明らかな大脳白質病変を有する群（PVH grade 2, 3）	P 値	明らかな大脳白質病変を有さない群（DWMH grade 0, 1）	明らかな大脳白質病変を有する群（DWMH grade 2, 3）	P 値
合計 iv∫	15.2（±1.60）	18.1（±1.91）	0.263	15.7（±1.86）	17.0（±1.63）	0.635
患者さんは，必要以上に世話を求めてくると思いますか iv∫	0.4（±0.10）	0.6（±0.12）	0.487	0.4（±0.11）	0.6（±0.10）	0.293
介護のために自分の時間が十分にとれないと思いますか iv∫	0.7（±0.11）	0.7（±0.13）	0.940	0.6（±0.12）	0.7（±0.11）	0.691
介護のほかに，家事や仕事などもこなしていかなければならず「ストレスだな」と思うことがありますか iv∫	0.8（±0.11）	0.8（±0.13）	0.903	0.9（±0.13）	0.8（±0.11）	0.439
患者さんの行動に対し，困ってしまうと思うことがありますか iv∫	1.0（±0.12）	1.0（±0.14）	0.950	1.0（±0.14）	1.1（±0.12）	0.537
患者さんのそばにいると腹がたつことがありますか iv∫	1.0（±0.10）	1.0（±0.12）	0.903	0.9（±0.12）	1.0（±0.11）	0.483
介護があるので家族や友人と付き合いづらくなっていると思いますか iv∫	0.5（±0.10）	0.5（±0.12）	0.859	0.4（±0.12）	0.6（±0.10）	0.390
患者さんが将来どうなるのか不安になることがありますか iv∫	1.5（±0.12）	1.7（±0.15）	0.308	1.5（±0.14）	1.7（±0.12）	0.439
患者さんがあなたに頼っていると思いますか iv∫	1.7（±0.14）	2.1（±0.16）	0.045*	1.8（±0.16）	2.0（±0.14）	0.435
患者さんのそばにいると，気が休まらないと思いますか iv∫	0.8（±0.12）	0.9（±0.14）	0.531	0.9（±0.14）	0.8（±0.12）	0.839
介護のために，体調を崩したと思ったことがありますか iv∫	0.3（±0.08）	0.3（±0.10）	0.571	0.3（±0.10）	0.3（±0.08）	0.933
介護があるので自分のプライバシーを保つことができないと思いますか iv∫	0.3（±0.07）	0.2（±0.08）	0.949	0.3（±0.08）	0.2（±0.07）	0.222
介護があるので自分の社会参加の機会が減ったと思うことがありますか iv∫	0.3（±0.09）	0.5（±0.11）	0.284	0.3（±0.11）	0.4（±0.09）	0.400
患者さんが家にいるので，友達を自宅に呼びたくても呼べないと思ったことがありますか iv∫	0.4（±0.10）	0.5（±0.12）	0.564	0.4（±0.12）	0.5（±0.11）	0.569
患者さんは「あなただけが頼り」というふうにみえますか iv∫	1.0（±0.15）	1.5（±0.17）	0.028*	1.1（±0.17）	1.3（±0.15）	0.364
今の暮らしを考えれば，介護にかける金銭的な余裕はないと思うことがありますか iv∫	0.5（±0.11）	0.8（±0.13）	0.061	0.6（±0.12）	0.7（±0.11）	0.438
介護にこれ以上の時間はさけないと思うことがありますか iv∫	0.5（±0.11）	0.6（±0.13）	0.681	0.6（±0.12）	0.6（±0.11）	0.998
介護が始まって以来，自分の思い通りの生活ができなくなったと思うことがありますか iv∫	0.5（±0.11）	0.7（±0.13）	0.278	0.6（±0.13）	0.6（±0.11）	0.937
介護を誰かにまかせてしまいたいと思うことがありますか iv∫	0.5（±0.11）	0.6（±0.13）	0.640	0.6（±0.13）	0.5（±0.11）	0.781
患者さんに対して，どうしていいかわからないと思うことがありますか iv∫	0.7（±0.11）	1.0（±0.14）	0.195	0.7（±0.13）	0.9（±0.12）	0.193
自分は今以上にもっと頑張って介護するべきだと思うことがありますか iv∫	0.5（±0.09）	0.6（±0.11）	0.702	0.6（±0.10）	0.5（±0.09）	0.669
本当は自分はもっとうまく介護できるのになあと思うことがありますか iv∫	0.5（±0.09）	0.5（±0.10）	0.500	0.7（±0.10）	0.4（±0.09）	0.008*
全体を通してみると，介護をするということはどれくらい自分の負担になっていると思いますか iv∫	0.9（±0.11）	1.0（±0.13）	0.543	1.0（±0.13）	0.9（±0.11）	0.758

iv 平均値（標準誤差）
∫ANCOVA　*P＜0.05

関して，背景の比較で有意な差が確認された高血圧の有無，降圧薬の服用の有無，下剤の服用の有無，睡眠薬の服用の有無，内服薬種類数の影響を検討するため，DWMH の明らかな大脳白質病変の有無，年齢を含めて多変量解析を行った．

転倒スコア 21 項目の下位項目の「もの忘れが気になりますか」の項目では DWMH の明らかな大脳白質病変の有無が影響しており（OR：0.36, 95%CI：0.16～0.81,

$p<0.05$)，その他の項目は有意な影響を認めなかった．

Dementia Behavior Disturbance Scale の下位項目の「昼間寝てばかりいる」では内服薬種類数が影響しており（標準偏回帰係数：0.261，$p<0.01$），その他の項目は有意な影響を認めなかった．

Zarit Careburden Scale の下位項目の「本当は自分はもっとうまく介護できるのになあと思うことがありますか」では有意な影響を認める項目はなかった．

考　察

明らかな大脳白質病変を有する群と有さない群の背景では，PVH，DWMH ともに年齢は明らかな大脳白質病変を有する MCI の方が高かった．性別，MMSE には差はなかった．年齢に関しては，大脳白質病変は加齢に伴って頻度が増加する[16]年齢は大脳白質病変の危険因子である[17]といったこれまでの報告と同様の結果となった．このため，本研究では年齢で調整し解析を行った．大脳白質病変と性差に関しては女性に多く認められる[18]といった報告や女性に多く認められるのは男性より高齢である影響による可能性がある[19]といった報告もあり統一された見解は得られていない．我々の報告では性差は認められなかった．

今回は詳細に検討を行うため高齢者総合機能評価の各検査において合計点の他，下位項目に関しても比較を行った．手段的 ADL の下位項目の自分の服薬管理で，明らかな大脳白質病変を有する群で自己管理が難しくなってきていた．認知機能低下と ADL の機能の低下の間には相関があり，発達の獲得と逆の順序で起こる[20]，血管性認知症においても同様の関係がある[21]といった報告がある．今回の我々の結果から，MCI の段階においても，大脳白質病変の存在により手段的 ADL の機能低下が発生し，日常生活を行う上での問題が出現しはじめている可能性が示唆された．

大脳白質病変と転倒や不安定性には関連がある[22]との報告がある．今回行った検討においても，転倒スコア 21 項目では明らかな大脳白質病変を有する群で高い傾向があり，転倒のリスクが認められた．MCI の段階でも大脳白質病変の存在により転倒の危険性を有することが示唆された．

高齢者のうつスケールである Geriatric Depression Scale では大脳白質病変を有する方が高い傾向が認められた．大脳白質病変とうつが関連する[23]といった報告があるが，うつ傾向が MCI の段階でも大脳白質病変を有する群で認められていることが示唆された．

血管性認知症においては，アパシー，意欲低下といった症状が頻度の高い症状であり，アルツハイマー型認知症と比較しても頻度の高い症状である[24]との報告があるが，今回用いた意欲の指標である Vitality Index では，MCI の段階では，大脳白質病変の有無で特徴の違いは認められなかった．

Dementia Behavior Disturbance Scale，Zarit Careburden Scale ともに，合計点では有意な差を認めないものの，下位項目で大脳白質病変の有無により有意な差を認めた．アルツハイマー型認知症と血管性認知症の周辺症状の重症度を比較した研究では，アルツハイマー型認知症と血管性認知症で周辺症状に明らかな相違を認めないが，認知症の重症度と周辺症状が相関する[25]といった報告や，アルツハイマー型認知症と血管性認知症の周辺症状を Neuropsychiatric Inventory：NPI で評価したところ血管性認知症で抑うつが有意に多かった[26]との報告もある．今回，MCI の段階で，大脳白質病変の有無により Dementia Behavior Disturbance Scale，Zarit Careburden Scale の下位項目に違いが認められた．

明らかな大脳白質病変の有無により，MCI の段階で ADL の低下傾向，転倒の危険性，うつ傾向，行動変化の出現といった特徴の違いがあり，この事実が，実際に介護負担として反映されている可能性が示唆されると考えられた．介護負担に関しては，アルツハイマー型認知症において認知機能が低いほど介護負担が大きい[27]という報告があるが，本研究において明らかな大脳白質病変を有する群では，MCI の段階で介護者の介護負担が増加している可能性が考えられた．

PVH と DWMH に関しては多くの共通項目で結果が一致したが，PVH に関して有意差がつく項目が多く，MCI の段階での徴候や症状をより鋭敏に相関している可能性が示唆された．

今回，認知症の前段階である MCI の時期に大脳白質病変の有無で臨床症状の違いを検出した研究としては今までにない報告である．また本研究では介護者に対する負担度についても高齢者総合機能評価を用い定量的・定性的に評価できた．

この結果は，患者本人や介護者に対し認知機能低下以外の症状の説明や理解に用いることができ，適切かつ，

よりクオリティーの高い介護や治療の介入の可能性に繋げることができると考えられた.

Study limitations

今回の研究では，大脳白質病変の有無による検討を行うため，大きく影響を及ぼすような粗大な脳梗塞を有する患者を除外した．ラクナ梗塞に関しては，大脳白質病変とラクナ梗塞は混在することが多い[28]といった報告もあり，今回の検討でもほぼ全例で無症候性ラクナ梗塞の合併を認めた.

アルツハイマー型認知症や，その他の疾患に伴う認知症に関しては初診時点での臨床症状，MRIによる海馬萎縮や脳血流シンチグラフィーによる疾患に特有の血流パターンをもとに，早期のアルツハイマー型認知症，前頭側頭型認知症，レビー小体型認知症等を除外しえたと考えているが，今回の研究では縦断的な経過は追っていない.

Amnestic MCI，Non-amnestic MCIの診断に関し，認知症疾患治療ガイドライン[29]においても，未だamnesiaの具体的な診断方法・基準が存在しないため，今回は検討を行っていない.

結　語

今回，MCIの段階における大脳白質病変の有無による臨床症状や介護負担の特徴を高齢者総合機能評価により詳細かつ精密に描出することができた．大脳白質病変を有する場合にMCIの段階からうつ傾向が認められ，服薬管理が困難になってくる傾向が確認された．また，昼間寝てばかりいるといった行動変化の出現もあり介護負担の違いに反映される可能性が示唆された．このような特徴を介護者に伝えることで，大脳白質病変を有するMCI患者や認知症患者のケアに対する効果的なアプローチが可能になると考えられた．また，介護者が患者の介護者自身への依存感を感じているといった傾向も確認され，介護破綻を防ぐ意味からも無理のない介護の継続のために，このような特徴を伝えることも重要であると考えられた．本研究から得られた結果は介護計画上，治療計画上ともに意義深く極めて重要であると考えられた.

文献

1) Looi JC, Sachdev PS: Differentiation of vascular dementia from AD on neuropsychological tests. Neurology 1999; 53: 670–678.
2) Sultzer DL, Levin HS, Mahler ME, High WM, Cummings JL: A comparison of psychiatric symptoms in vascular dementia and Alzheimer's disease. Am J Psychiatry 1993; 150: 1806–1812.
3) Tullberg M, Fletcher E, DeCarli C, Mungas D, Reed BR, Harvey DJ, et al.: White matter lesions impair frontal lobe function regardless of their location. Neurology 2004; 63: 246–253.
4) Robertsson B, Blennow K, Gottfries CG, Wallin A: Delirium in dementia. Int J Geriatr Psychiatry 1998; 13: 49–56.
5) Staekenborg SS, van der Flier WM, van Straaten EC, Lane R, Barkhof F, Scheltens P: Neurological signs in relation to type of cerebrovascular disease in vascular dementia. Stroke 2008; 39: 317–322.
6) Poggesi A, Pracucci G, Chabriat H, Erkinjuntti T, Fazekas F, Verdelho A, et al.: Leukoaraiosis And DISability Study Group: Urinary complaints in nondisabled elderly people with age-related white matter changes: the Leukoaraiosis And DISability (LADIS) Study. J Am Geriatr Soc 2008; 56: 1638–1643.
7) Sakakibara R, Hattori T, Uchiyama T, Yamanishi T: Urinary function in elderly people with and without leukoaraiosis: relation to cognitive and gait function. J Neurol Neurosurg Psychiatry 1999; 67: 658–660.
8) Vermeer SE, Hollander M, van Dijk EJ, Hofman A, Koudstaal PJ, Breteler MM; Rotterdam Scan Study: Silent brain infarcts and white matter lesions increase stroke risk in the general population: the Rotterdam Scan Study. Stroke 2003; 34: 1126–1129.
9) Mosley TH Jr, Knopman DS, Catellier DJ, Bryan N, Hutchinson RG, Grothues CA, et al.: Cerebral MRI findings and cognitive functioning: the Atherosclerosis Risk in Communities study. Neurology 2005; 64: 2056–2062.
10) Yao H, Takashima Y, Mori T, Uchino A, Hashimoto M, Yuzuriha T, et al.: Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study. Hypertens Res 2009; 32: 586–590.
11) Doddy RS, Massman PJ, Mawad M, Nance M: Cognitive consequences of subcortical magnetic resonance imaging changes in Alzheimer's disease: comparison to small vessel ischemic vascular dementia. Neuropsychiatry Neuropsychol Behav Neurol 1998; 11: 191–199.
12) Murray ME, Senjem ML, Petersen RC, Hollman JH, Preboske GM, Weigand SD, et al.: Functional impact of white matter hyperintensities in cognitively normal eld-

erly subjects. Arch Neurol 2010; 67: 1379–1385.
13) Petersen RC: Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256: 183–194.
14) 日本脳ドック学会　脳ドックの新ガイドライン作成委員会編：脳ドックのガイドライン 2014，改訂第4版，響文社，2014，p38–47.
15) Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA: MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol 1987; 149: 351–356.
16) Schmidt R, Lechner H, Fazekas F, Niederkorn K, Reinhart B, Grieshofer P, et al.: Assessment of cerebrovascular risk profiles in healthy persons: definition of research goals and the Austrian Stroke Prevention Study (ASPS). Neuroepidemiology 1994; 13: 308–313.
17) Park K, Yasuda N, Toyonaga S, Yamada SM, Nakabayashi H, Nakasato M, et al.: Significant association between leukoaraiosis and metabolic syndrome in healthy subjects. Neurology 2007; 69: 974–978.
18) de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R, et al.: Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001; 70: 9–14.
19) Simoni M, Li L, Paul NL, Gruter BE, Schulz UG, Küker W, et al.: Age- and sex-specific rates of leukoaraiosis in TIA and stroke patients: population-based study. Neurology 2012; 79: 1215–1222.
20) 清水　一，吉川ひろみ，山口晴保ほか：知的退行の機能年齢水準への反映．作業療法　1991; 10: 291–299.
21) 久野真矢，前川正雄，武内　淳ほか：血管性認知症，アルツハイマー型認知症の認知機能と発達に基づいたADL能力の関連．老年精神医学雑誌　2012; 23: 837–845.
22) Zheng JJ, Delbaere K, Close JC, Sachdev PS, Lord SR, et al.: Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. Stroke 2011; 42: 2086–2090.
23) Firbank MJ, O'Brien JT, Pakrasi S, Pantoni L, Simoni M, Erkinjuntti T, et al.: White matter hyperintensities and depression—preliminary results from the LADIS study. Int J Geriatr Psychiatry 2005; 20: 674–679.
24) Ikeda M, Fukuhara R, Shigenobu K, Hokoishi K, et al.: Dementia associated mental and behavioural disturbances in elderly people in the community: findings from the first Nakayama study. J Neurol Neurosurg Psychiatry 2004; 75: 146–148.
25) Thompson C, Brodaty H, Trollor J, Sachdev P: Behavioral and psychological symptoms associated with dementia subtype and severity. Int Psychogeriatr 2010; 22: 300–305.
26) Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, et al.: Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry 2000; 157: 708–714.
27) Kamiya M, Sakurai T, Ogama N, Maki Y, Toba K: Factors associated with increased caregivers' burden in several cognitive stages of Alzheimer's disease. Geriatr Gerontol Int 2014; 2: 45–55.
28) Wardlaw JM, Doubal F, Armitage P, Chappell F, Carpenter T, Muñoz Maniega S, et al.: Lacunar stroke is associated with diffuse blood-brain barrier dysfunction. Ann Neurol 2009; 65: 194–202.
29) 日本神経学会監修　認知症疾患治療ガイドライン作成合同委員会編：認知症疾患治療ガイドライン 2010，第1版，医学書院，2010，p188–189.

ORIGINAL ARTICLE

The characteristics of a comprehensive geriatric assessment in patients with mild cognitive impairment with a cerebral white matter lesion

Toshimasa Obara, Hiroshi Hasegawa, Yoshitaka Wachi, Masamichi Tanaka, Michiko Sato, Yoshio Kobayashi, Hitomi Koshiba, Kumiko Nagai, Yukiko Yamada, Toshifumi Matsui and Koichi Kozaki

Abstract

Aim: Vascular dementia may be referred to as "treatable dementia" because its development and progress can be inhibited by intervention in the early stage. In particular, cerebral white matter lesions are readily encountered the clinical setting. In this study, we aimed to clarify the phenomenon and symptoms of patients with mild cognitive impairment (MCI) with cerebral white matter lesions prior to the onset of dementia.

Methods: The subjects included 181 cases diagnosed with MCI among 643 consecutive new patients of the Center for Comprehensive Care on Memory Disorder at Kyorin University Hospital from January 1, 2013 to January 31, 2014. Patients with particular diseases were excluded. An interview, physical examination, comprehensive geriatric assessment, brain MRI and SPECT were performed for all subjects. The cerebral white matter lesions were evaluated using the modified Fazekas scale. We defined Grades 0 and 1 as the group without apparent cerebral white matter lesions and Grades 2 and 3 as the group with apparent cerebral white matter lesions. We compared the laboratory findings and outcomes of these two groups.

Results: The age of the group with apparent cerebral white matter lesions was significantly higher than the group without apparent cerebral white matter lesions ($P<0.05$). No significant difference was observed regarding gender, MMSE, or "vegetable" term retrieval. A significant difference was observed in the total score and the subordinate component of the 21-item fall risk index and geriatric depression scale between the groups ($P<0.05$). Additionally, a significant difference was observed regarding the subordinate component of the instrumental ADL, the Dementia Behavior Disturbance Scale and the Zarit Care Burden Scale between the groups ($P<0.05$).

Conclusions: Our results suggest that the presence of white matter lesions at the stage of MCI has a significant relationship to care burden due to the deterioration of ADL, risk of falling, and the presence of depression and behavior disorders. We speculate that our results are useful for the explanation of the characteristics of MCI with white matter lesion to the patients and the care givers. Furthermore, these results may lead to improvements in the appropriate approach, intervention and appropriate nursing of such patients.

Key words: Cerebral white matter lesion, Comprehensive geriatric assessment, Mild cognitive impairment, Dementia Behavior Disturbance Scale, Zarit Care Burden Scale

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Correlation between the serum eicosapentanoic acid-to-arachidonic acid ratio and the severity of cerebral white matter hyperintensities in older adults with memory disorder

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Aim: The relationships of n-3 polyunsaturated fatty acids, such as docosahexaenoic acid and eicosapentaenoic acid (EPA), to stroke and cardiovascular events have been studied extensively. The present study was undertaken to analyze the relationships of the severity of cerebral white matter hyperintensities (WMH) to the blood polyunsaturated fatty acids level and the ratio of serum EPA level to the serum arachidonic acid (AA) level (EPA/AA ratio) among older adults.

Methods: A total of 150 patients underwent diagnostic magnetic resonance imaging and blood sampling under the fasting state. In regard to WMH, the periventricular hyperintensities and deep white matter hyperintensities were rated according to the Fazekas classification. The serum docosahexaenoic acid, EPA, AA, dihomo-γ-linolenic acid and EPA/AA ratio were compared in relation to the grade of severity of WMH. Furthermore, multiple regression analysis was carried out with age, sex and atherosclerosis risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking status) as the covariables, serum polyunsaturated fatty acids level as an independent variable and Fazekas grade as the dependent variable.

Results: A rise of the periventricular hyperintensities grade was associated with a significant reduction of the mean EPA level ($P < 0.05$) and EPA/AA ratio ($P < 0.05$). The multiple regression analysis identified a significant negative correlation between the periventricular hyperintensities grade and the serum EPA/AA ratio ($\beta = -0.215$, $P < 0.05$).

Conclusion: These results suggest that the serum EPA/AA ratio have an important role in the formation and progression of WMH. **Geriatr Gerontol Int 2015; 15 (Suppl. 1): 48–52.**

Keywords: eicosapentaenoic acid, eicosapentaenoic acid/arachidonic acid, leukoaraiosis, polyunsaturated fatty acids, white matter hyperintensity.

Introduction

In recent years, many studies have been carried out to identify the role of polyunsaturated fatty acids (PUFA). In connection with atherosclerosis, n-3 PUFA, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to have antithrombotic activity, and high blood levels of n-3 PUFA have been shown to be associated with a lower incidence of sudden cardiac death,[1] whereas arachidonic acid (AA; n-6 PUFA) has been shown to induce platelet aggregation and inflammation.[2] The ratio of the serum EPA level to the serum AA level (EPA/AA ratio) can serve as an indicator of the risk for cardiovascular events.[3] In view of these findings and other reports, PUFA are considered to play important roles in the onset/progression of atherosclerotic disease. If we consider the report that chronic atherosclerosis underlies the formation of leukoaraiosis; that is, cerebral white matter hyperintensity (WMH), it is assumed that an association between the serum PUFA levels and the severity of WMH exists.[4] The present study was undertaken to analyze the relationships between the serum levels of PUFA and the severity of WMH through investigation of the severity of WMH and measurement of the serum PUFA levels and EPA/AA ratios in outpatients visiting our Center for Comprehensive Care on Memory Disorders, Tokyo, Japan, for the first time.

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Material and methods

Patients

A total of 150 patients who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital for the first time were enrolled in the present study. The study was carried out with the approval of the ethics committee of Kyorin University (179-06). We explained the study to all the participants and their families, and obtained written informed consent. We handled all the data carefully to keep the participants' anonymity and protect their privacy. We excluded patients who had a history of treatment with oral purified EPA and/or a history of stroke.

Magentic resonance imaging

Magnetic resonance imaging (MRI) was carried out on a 1.5-T scanner (Toshiba Medical Systems, Tochigi, Japan). T1-weighted images (repetition time [TR] = 496 ms, echo time [TE] = 12 ms), T2-wighted images (TR = 4280 ms, TE = 105 ms) and fluid-attenuated inversion recovery-weighted images (TR = 8000 ms, TE = 105 ms, 5 mm slice thickness) were obtained in the axial plane.

Periventricular hyperintensity and deep WMH scores

WMH was separately rated as periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) using the modified Fazekas scale.[5] The PVH severity was graded as follows: 0 = absent; 1 = cap or pencil-thin lining; 2 = smooth halo; and 3 = irregular PVH extending into the deep white matter. The DWMH severity was rated as follows: 0 = absence; 1 = punctuate foci; 2 = beginning confluence of foci; and 3 = large confluent areas.

Laboratory tests

Blood samples were obtained in the morning. The serum fatty acid composition, including the levels of EPA, DHA, dihomo-γ-linolenic acid (DGLA) and AA, was measured by gas chromatography at a commercially available laboratory (SRL, Tokyo, Japan).

Statistical analysis

Statistical analysis was carried out using SPSS version 22.0 (IBM, Armonk, NY, USA). To evaluate the differences in the grade of WMH, analysis of variance (ANOVA) was carried out for continuous variables, and the χ^2-test was used for categorical variables. Multiple linear regression analysis was carried out using the grade of PVH and DWMH as the dependent variables, and age, sex, vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia and smoking status) and serum fatty acid profile as independent variables.

Results

The characteristics of the study participants are shown in Table 1. In the one-way ANOVA, a rise of the PVH grade was associated with a significant reduction of the mean serum EPA level ($P < 0.05$) and EPA/AA ratio ($P < 0.05$; Fig. 1a), whereas it showed no significant association with the serum level of DHA, DGLA or AA. No significant association was observed between the DWMH grade and the serum DGLA, AA, EPA, DHA or EPA/AA ratio (Table 2). In the analysis of the association of the PVH and DWMH grades with the other risk factors for atherosclerosis, smoking history was correlated with the PVH (χ^2-test, $P < 0.05$; Table 2) and DWMH (χ^2-test, $P = 0.069$; Table 3) severity.

Multiple regression analysis carried out using the severity of the PVH and DWMH grades as a dependent variable, and the age, sex and atherosclerosis risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking status) as covariables showed a significant negative correlation between the PVH grade and the serum EPA/AA ratio ($\beta = -0.215$, $P < 0.05$), and a tendency towards a negative correlation (not statistically significant) between the DWMH grade and the serum EPA/AA ratio ($\beta = -0.164$, $P = 0.085$; Table 4).

Table 1 Demographic characteristics of the patients

total n = 150	
Age, years	79.6 ± 5.8
Female, n (%)	91 (61%)
BMI	21.4 ± 3.1
MMSE, points (/30)	22.9 ± 5.2
Hypertension, yes, n (%)	67 (45%)
Diabetes, yes, n (%)	24 (16%)
Hyperlipidemia, yes, n (%)	44 (29%)
Smoking, yes, n (%)	
current	4 (3%)
past	26 (17%)
never	120 (80%)
Serum DGLA, μg/mL	35.2 ± 10.7
Serum AA, μg/mL	180 ± 42.4
Serum EPA, μg/mL	94 ± 51.1
Serum DHA, μg/mL	154.1 ± 43.9
Serum EPA/AA ratio	0.55 ± 0.36

BMI, body mass index; MMSE, mini mental state examination; DGLA, dihomogammmalinolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

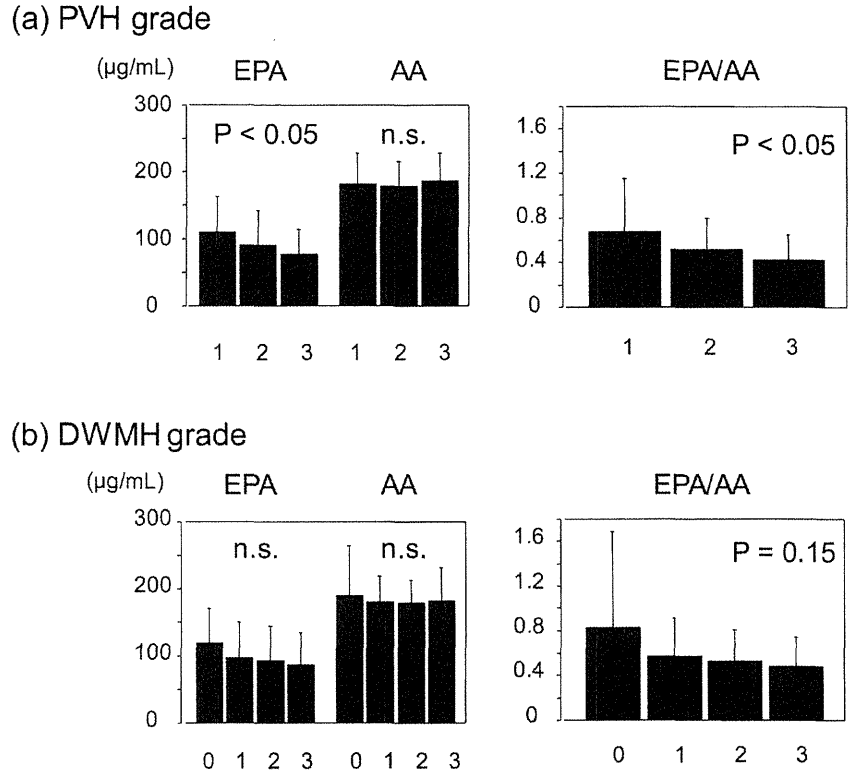

Figure 1 Eicosapentaenoic acid (EPA) and arachidonic acid (AA) levels and EPA/AA ratio analyzed by the grade of severity of the white matter lesions (ANOVA).

Table 2 Relationship between the grade of the periventricular hyperintensity and other parameters

PVH class (Fazekas)	0 (n = 0)	1 (n = 49)	2 (n = 74)	3 (n = 27)	p value
Age, years	–	78.5 ± 5.6	79.8 ± 5.9	81.4 ± 5.7	0.109
MMSE, points (/30)	–	23.6 ± 4.9	23.1 ± 5.0	21.2 ± 5.9	0.140
Female, n (%)	–	32 65.3%	44 59.5%	15 55.6%	0.676
Hypertension, yes, n (%)	–	16 32.7%	39 52.7%	12 44.4%	0.117
Diabetes, yes, n (%)	–	10 20.4%	12 16.2%	2 7.4%	0.318
Hyperlipidemia, yes, n (%)	–	16 32.7%	22 29.7%	6 22.2%	0.630
Smoking, yes, n (%)	–				0.042
current	–	0 0.0%	1 1.4%	3 11.1%	
past	–	10 20.4%	13 17.6%	3 11.1%	
never	–	39 79.6%	60 81.1%	21 77.8%	
Serum DGLA, μg/mL	–	34.7 ± 10.9	34.0 ± 10.4	38.7 ± 10.6	0.210
Serum AA, μg/mL	–	180.5 ± 47.9	177.5 ± 38.8	185.4 ± 42.6	0.762
Serum EPA, μg/mL	–	109.6 ± 53.6	90.5 ± 51.9	76.7 ± 37.5	0.042
Serum DHA, μg/mL	–	162.5 ± 38.8	152.6 ± 44.1	143.9 ± 50.5	0.275
Serum EPA/AA ratio	–	0.674 ± 0.483	0.517 ± 0.277	0.425 ± 0.219	0.021

Discussion

In patients with cardiovascular disease, low serum level of EPA and low EPA/AA ratio have been reported to serve as risk factors for cognitive impairment.[6] When taken together with the previous report of a significant association between the severity of leukoaraiosis and decreased cognitive functions, the results of the present study suggest that low serum EPA level will compromise the cognitive function mediated by WMH.[7,8]

Furthermore, considering the report that a low serum EPA level is a risk factor for intracerebral hemorrhage,[9] and that the presence of WMH is also one of the risk factors for intracerebral hemorrhage,[10,11] it is assumed

Table 3 Relationship between the deep white matter hyperintensity grade and other parameters

DWMH class (Fazekas)	0 (n = 8)	1 (n = 55)	2 (n = 53)	3 (n = 31)	p value
Age, years	76.6 ± 6.0	79.5 ± 5.5	79.7 ± 6.4	80.5 ± 5.5	0.438
MMSE, points (/30)	23.8 ± 4.7	22.3 ± 5.6	23.4 ± 5.0	22.8 ± 5.3	0.739
Female, n (%)	6 75.0%	32 58.2%	35 66.0%	15 48.4%	0.338
Hypertension, yes, n (%)	2 25.0%	19 34.5%	25 47.2%	18 58.1%	0.148
Diabetes, yes, n (%)	0 0.0%	11 20.0%	6 11.3%	7 22.6%	0.232
Hyperlipidemia, yes, n (%)	4 50.0%	14 25.5%	16 30.2%	9 29.0%	0.558
Smoking, yes, n (%)					0.069
current	0 0.0%	0 0.0%	1 1.9%	3 9.7%	
past	3 37.5%	12 21.8%	6 11.3%	5 16.1%	
never	5 62.5%	43 78.2%	46 86.8%	23 74.2%	
Serum DGLA, μg/mL	33.1 ± 13.3	34.9 ± 10.6	34.6 ± 9.7	37.2 ± 12.0	0.741
Serum AA, μg/mL	188.8 ± 75.2	179.0 ± 40.0	178.5 ± 34.1	181.1 ± 49.6	0.945
Serum EPA, μg/mL	118.6 ± 51.0	96.6 ± 52.6	91.8 ± 51.8	86.4 ± 48.6	0.513
Serum DHA, μg/mL	168.1 ± 27.2	155.6 ± 41.2	158.3 ± 40.4	140.6 ± 56.6	0.340
Serum EPA/AA ratio	0.824 ± 0.862	0.572 ± 0.337	0.525 ± 0.282	0.479 ± 0.262	0.147

Table 4 Multiple regression analysis for determinants of the grade of PVH and DWMH

	for PVH (R^2 = 0.173; $p < 0.01$) β	p value	for DWMH (R^2 = 0.186; $p < 0.01$) β	p value
Age, years	0.118	0.210	0.074	0.430
Sex	−0.106	0.271	−0.100	0.296
Hypertension	0.155	0.101	0.278	0.004
Diabetes	−0.090	0.352	0.063	0.517
Hyperlipidemia	−0.078	0.417	−0.076	0.428
Current smoker	0.217	0.022	0.219	0.020
Serum EPA/AA ratio	−0.215	0.026	−0.164	0.085

that low serum EPA is associated with greater WMH and serves as a risk factor for intracerebral hemorrhage.

The mechanisms by which EPA protects the brain include its anticoagulant activity during ischemic stroke, alleviation of post-ischemic oxidative stress, reduction of Rho-kinase activation,[12] alleviation of inflammatory reactions[13] and so on. Because elevation of oxidative stress has also been reported to be correlated with the WMH volume, EPA might be considered to have an influence in suppressing the onset and progression of WMH.[14]

N-3 and n-6 PUFA need to be taken from the diet, and blood EPA and DHA levels are in proportion to the amounts of EPA and DHA ingested.[15] Although active ingestion of EPA is important for preventing WMH, there is a report that smokers show lower serum EPA levels and EPA/AA ratios than non-smokers.[16] In the present study also, multiple regression analysis carried out to determine the PVH and DWMH grade showed a great influence of the EPA/AA ratio and the current smoking status (Table 4). This result indicates that not only advice on dietary habits, but on the cessation of smoking is important in the prevention of the progression of WMH.

A major limitation of the present study was the cross-sectional analysis. Longitudinal study is required to elucidate the relationship between the progression of WMH and low serum levels of EPA and EPA/AA ratio. We should also investigate the patient's eating habits to know the influence on serum levels of n-3 and n-6 PUFA.

Low blood EPA level and EPA/AA ratio were found to be associated with the PVH grade, and to serve as a risk factor for WMH. These results suggest that the EPA/AA ratio plays an important role in the formation and progression of WMH.

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Disclosure statement

The authors declare no conflict of interest.

References

1 Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. *J Am Coll Cardiol* 2009; **54**: 585–594.
2 Martinelli N, Consoli L, Olivieri O. A 'desaturase hypothesis' for atherosclerosis: janus-faced enzymes in omega-6 and omega-3 polyunsaturated fatty acid metabolism. *J Nutrigenet Nutrigenomics* 2009; **2**: 129–139.
3 Ohnishi H, Saito Y. Eicosapentaenoic acid (EPA) reduces cardiovascular events: relationship with the EPA/arachidonic acid ratio. *J Atheroscler Thromb* 2013; **20**: 861–877.
4 Ben-Assayag E, Mijajlovic M, Shenhar-Tsarfaty S, Bova I, Shopin L, Bornstein NM. Leukoaraiosis is a chronic atherosclerotic disease. *ScientificWorldJournal* 2012; **2012**: 532141.
5 Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol* 1987; **149**: 351–356.
6 Yagi S, Hara T, Ueno R *et al.* Serum concentration of eicosapentaenoic acid is associated with cognitive function in patients with coronary artery disease. *Nutr J* 2014; **14**: 112.
7 Pantoni L. New evidence in the field of white matter changes. *No to Shinkei* 2006; **58**: 298–302.
8 Chutinet A, Rost NS. White matter disease as a biomarker for long-term cerebrovascular disease and dementia. *Curr Treat Options Cardiovasc Med* 2014; **16**: 292.
9 Ikeya Y, Fukuyama N, Mori H. Low plasma eicosapentaenoic acid concentration as a possible risk factor for intracerebral hemorrhage. *Nutr Res* 2015; **35**: 214–220.
10 Pantoni L, Fierini F, Poggesi A. Thrombolysis in acute stroke patients with cerebral small vessel disease. *Cerebrovasc Dis* 2014; **37**: 5–13.
11 Neumann-Haefelin T, Hoelig S, Berkefeld J *et al.* Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke. *Stroke* 2006; **37**: 2463–2466.
12 Ueda M, Inaba T, Nito C, Kamiya N, Katayama Y. Therapeutic impact of eicosapentaenoic acid on ischemic brain damage following transient focal cerebral ischemia in rats. *Brain Res* 2013; **1519**: 95–104.
13 Okabe N, Nakamura T, Toyoshima T, Miyamoto O, Lu F, Itano T. Eicosapentaenoic acid prevents memory impairment after ischemia by inhibiting inflammatory response and oxidative damage. *J Stroke Cerebrovasc Dis* 2011; **20**: 188–195.
14 Corbin ZA, Rost NS, Lorenzano S *et al.* White matter hyperintensity volume correlates with matrix metalloproteinase-2 in acute ischemic stroke. *J Stroke Cerebrovasc Dis* 2014; **23**: 1300–1306.
15 Titova OE, Sjögren P, Brooks SJ *et al.* Dietary intake of eicosapentaenoic and docosahexaenoic acids is linked to gray matter volume and cognitive function in elderly. *Age (Omaha)* 2013; **35**: 1495–1505.
16 Okada K, Kotani K, Yagyu H, Ishibashi S. Eicosapentaenoic acid/arachidonic acid ratio and smoking status in elderly patients with type 2 diabetes mellitus. *Diabetol Metab Syndr* 2014; **6**: 85.

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ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Interview- and questionnaire-based surveys on elderly patients' wishes about artificial nutrition and hydration during end-of-life care

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Aim: To promote advance directives, it is crucial to understand how many older persons have wishes related to end-of-life care. Additionally, it is important to understand how cognitive function or mood affect these wishes.

Methods: For the interview-based survey, 99 inpatients aged 75 years or older were enrolled after excluding patients with a Mini-Mental State Examination score of 20 or less. For the questionnaire-based survey, 99 outpatients aged 75 years or older without dementia were enrolled. Both surveys comprised the same items on older patients' wishes related to artificial nutrition and hydration (ANH) during end-of-life care.

Results: Of the total enrolled patients, 76.8% participated in the interviews. Of these, 50.0% were against ANH during their end-of-life care, including the patients who were definitely against ANH (26.3%). In contrast, just 5.3% wished to receive ANH. In the questionnaire survey, 65.6% of the respondents were against ANH, and 4.9% wished to receive ANH. Aging and Mini-Mental State Examination scores of less than 24 were significantly associated with a higher tendency to decline from participating in the interview. However, the distribution of the interview answers was not associated with age, Mini-Mental State Examination or Geriatric Depression Scale scores. Of the interviewed patients, 84.2% agreed to their responses being preserved in their medical records.

Conclusions: Although the majority of the elderly patients were against ANH during end-of-life care, many patients did not have definite wishes in Japan. The percentage of those who were against ANH was not associated with cognitive function or depressive state. **Geriatr Gerontol Int ••; ••: ••–••.**

Keywords: advance care planning, advance directive, artificial nutrition and hydration, end-of-life care, interview.

Introduction

The aged society makes it increasingly important to understand how to care for the elderly at the end stage of their lives.[1,2] One area of concern is that the majority of elderly patients with advanced dementia have trouble with nutrition as a result of loss of appetite or dysphagia.[3] Specifically, they frequently develop a fever and are finally diagnosed as unable to receive enough oral nutrition. In many cases in Japan, artificial nutrition and hydration (ANH) through gastrostomy, nasal tube or central venous catheter is initiated,[4,5] although the beneficial effects of any of these methods have not been reported in previous investigations.[6–8]

Contemporarily, many medical societies and doctors have shown great concern about the use of ANH in advanced dementia.[7] However, the caregivers and primary healthcare professionals of patients with dementia are challenged to forgo ANH, because this decision can directly relate to the patients' lives.[9,10]

Although advance directives can be very useful for caregivers and healthcare team members in deciding on the best patient end-of-life treatment,[8,11,12] they are not prevalent enough in Japan.[13,14] Various factors prevent elderly patients from making advance directives.[15] For

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Note: Supplementary information is available on the Geriatrics & Gerontology International website.

instance, elderly patients might not want to talk with family members, especially children, about their death. Furthermore, elderly patients might not have strong wishes about their future care.

To understand the usefulness of advance directives, we first need to know how many elderly patients have wishes about their own end-of-life care. However, most previous studies pertaining to thoughts about ANH during this stage have focused on younger people, such as healthcare professionals and community-dwelling adults.[14,16–18] We investigated elderly patients' own wishes regarding ANH for the time when they reached the end-of-life stage in the future. To reflect wishes related to advance directives, participants were informed that, if they consented, answers would be preserved in their medical records. In addition, we carried out a questionnaire-based survey to evaluate how interview-based methods affect answer distributions.

Methods

Study design

We carried out two styles of surveys on the wishes regarding ANH during end-of-life care; that is, interview- and questionnaire-based surveys. In the interview-based survey, a doctor interviewed elderly inpatients in a private room without any consultation with family members. The interview was carried out after the completion of scheduled examinations. Patients' consent was confirmed twice, once before and once after the interview. The latter one included consent about the preservation of answers in their medical records.

The questionnaire-based survey was carried out by providing elderly outpatients with a questionnaire with the same items as the interview-based survey. The completed questionnaires were mailed or returned to the researchers without identification of the respondent. Returning the survey was regarded as consent to survey participation. In the questionnaire-based survey, responses were not retained in medical records unless patients made this request.

The study protocol was approved by the institutional review board of the Graduate School of Medicine, University of Tokyo.

Participants

The participants of the interview-based survey were recruited consecutively from the population of inpatients aged 75 years or older admitted for examination at the Faculty of Geriatric Medicine, The University of Tokyo Hospital, Tokyo, Japan. Data collection occurred from September 2012 to June 2014. Patients admitted for emergencies for acute diseases were excluded. We also excluded patients whose prognosis was estimated to be less than 2 years for uncured malignant tumors and interstitial pneumonia. The Mini-Mental State Examination (MMSE), Geriatric Depression Scale (GDS), Barthel Index and Lawton Instrumental Activities of Daily Living (IADL) Index were administered to all potential participants, and those with a score of 20 or less on the MMSE were excluded. In addition, patients whose medical documents had shown some unreasonable complaints or anxieties about medical examination or intervention were excluded, as determined by the primary doctors or interviewers. Finally, 99 patients were requested to participate in the interview.

The participants of the questionnaire-based survey were recruited consecutively from the outpatients aged 75 years or older at the Faculty of Geriatric Medicine, The University of Tokyo Hospital from March 2014 to June 2014. The patients who had already been recruited to the interview survey were not enrolled in the questionnaire survey. Although the MMSE was not carried out on all outpatients, primary doctors judged patients' levels of cognitive function, and the patients with dementia were excluded. The other exclusion criteria were the same as those of the interview survey. Finally, the questionnaire was distributed to 99 patients.

Interview and questionnaire contents

The same items were used for both interview- and questionnaire-based surveys (Supplementary Appendix SI). In the interview survey, an interviewer read the explanations and questions with minor modifications for the oral approach and participant responses.

First, the background of the survey was explained. Subsequently, only in the interview survey, we informed participants that the answers would be preserved in their medical records, if they consented.

After explaining the effectiveness and complications of feeding through gastrostomy, nasal tube and intravenous hyperalimentation to participants (Supplementary Appendix SII), the questions were initiated as follows (Supplementary Appendix SI).

Assuming that the participant was in a state preventing his/her ability to walk, maintain conversation and eat enough, three questions were asked.

Question 1, "If necessary to live, would you like to start using a gastrostomy tube or nasal tube?" The response options were: answer 1, "I definitely want to start"; answer 2, "If anything, I want to start"; answer 3, "I don't know"; answer 4, "If anything, I do not want to start"; or answer 5, "I definitely do not want to start."

Question 2, "If necessary to live, would you like to start intravenous hyperalimentation?" The possible response options were the same as question 1.

Question 3, "Do you believe it is acceptable to die as the result of undernutrition?" The response options

were: answer 1, "Definitely unacceptable"; answer 2, "If anything, I would consider it unacceptable"; answer 3, "I don't know"; answer 4, "If anything, I would consider it acceptable"; or answer 5, "Definitely, acceptable."

Additionally, we asked participants if they had discussed ANH during end-of-life care with others.

Patient grouping based on participant responses to each question

Hereafter, patients who responded that they did not want to start tube feeding or intravenous hyperalimentation, and that it is acceptable to die as the result of undernutrition (i.e. chose answers 4 or 5 for all three questions) were referred to as the "No ANH" group. Among the "No ANH" group, some responded that they definitely did not want to start tube feeding or intravenous hyperalimentation, and that it is definitely acceptable to die as the result of undernutrition (i.e. chose answer 5 for all three questions). These patients were referred to as the "Definitely, No ANH" group. Patients who responded that they wanted to start tube feeding and intravenous hyperalimentation, and that it is not acceptable to die as the result of undernutrition were referred to as the "Pro ANH" group (i.e. chose answers 1 or 2 for all three questions). The other patients were referred to as the "Undecided" group; this group comprised the patients who chose answer 3 (I don't know) for some of questions 1, 2 and 3, and the patients who had inconsistent answers (i.e. chose answers 1 or 2 for some questions and answers 4 or 5 for the other questions).

Statistical analysis

Because all background data significantly deviated from normality as shown by the Shapiro–Wilk test, the Mann–Whitney *U*-test was used to compare interviewed patients and those that did not participate in the interview. The χ^2-test or Fisher's exact test was used to compare categorical variables, such as sex, the number of patients with each existing disease and answers to the questions about ANH. To determine the factors that influenced interview consent, the odds ratios (OR) and 95% confidence intervals (CI) were calculated using multiple logistic regression analysis. All statistical analyses were carried out using the SPSS software program (version 19.0; SPSS, Chicago, IL, USA). Statistical significance was defined as P-values < 0.05.

Results

Answer distribution in the interview-based and questionnaire-based surveys

In the interview-based survey, 126 patients were consecutively recruited as stable patients with MMSE scores of 21 or higher. A total of 18 patients were excluded because their medical records showed some unreasonable complaints or anxieties about medical examination or intervention. Nine patients were not interviewed because they had no time available. Among the remaining 99 patients who were requested to participate in the interview, 76 patients (76.8%) agreed to participate in the interview. Characteristics of these patients are shown in Table 1. The distributions of their responses to questions 1, 2 and 3 are shown in Table 2.

In the questionnaire-based survey, 104 patients were recruited as patients without dementia. Five patients were excluded because their medical records showed some unreasonable complaints or anxieties. The characteristics of the 99 enrolled patients are shown in Table 1. Of these 99 patients, 61 (61.6%) responded to the questionnaires. The distributions of their responses to questions 1, 2 and 3 are shown in Table 2.

The ratio of the patients who selected the option "I don't know" was higher for all the questions in the interview survey than it was in the questionnaire survey ($P = 0.07$, $P = 0.001$, $P < 0.001$, on question 1, 2 and 3, respectively). As for the other answers, the number of the patients against ANH (answers 4 and 5) per the number of the positive patients about ANH (answers 1 and 2) were not significantly different among questions 1, 2 and 3, or between the interview survey and questionnaire survey (Table 2).

To compare tube feeding and intravenous hyperalimentation, we also evaluated the answer combinations for questions 1 and 2. The number of inconsistent answers for questions 1 and 2 (i.e. chose answers 1 or 2 for one question, and answers 4 or 5 for the other question) was only one for both the interview survey and the questionnaire survey (Supplementary Table S1).

The patient grouping in the interview survey showed that the "No ANH" group comprised 38 patients (50.0% of the interviewed patients), including 20 patients from the "Definitely, No ANH" group (26.3% of the interviewed patients). The "Pro ANH" group had just four patients (5.3% of the interviewed patients). The "Undecided" group comprised the remaining 44.7% of the interviewed patients. The questionnaire survey showed that the "No ANH" group comprised 40 patients (65.6% of the patients who responded), including 22 patients from the "Definitely, No ANH" group (36.1% of the patients who responded). The "Pro ANH" group had just three patients (4.9% of the patients who responded; Supplementary Table S1).

Factors influencing interview consent and ANH answers

First, we evaluated the factors that influenced interview consent. We found that age, percentage of MMSE

Table 1 Baseline characteristics of the enrolled patients

	Interview Total $n = 99$	Interviewed $n = 76$	Non-interviewed $n = 23$	*P*-value	Questionnaire Total $n = 99$
Age (years)	81.5 (5.0)	80.9 (4.5)	83.3 (6.1)	0.100	80.6 (4.8)
Males/females	47/52	38/38	9/14	0.360	60/39
MMSE score	26.7 (2.5)	26.9 (2.4)	25.8 (2.5)	0.066	
MMSE score ≤23	11.1%	6.6%	26.1%	0.018	
GDS15	5.0 (3.4) ($n = 97$)	4.7 (3.1) ($n = 74$)	5.9 (4.1) ($n = 23$)	0.252	
GDS15 score ≥10	11.3%	8.1%	21.7%	0.082	
Barthel Index	94.3 (11.7) ($n = 96$)	94.5 (12.6) ($n = 74$)	93.9 (8.2) ($n = 22$)	0.223	
Lawton IADL (males)	4.4 (1.0) ($n = 46$)	4.6 (0.9) ($n = 37$)	3.7 (1.2) ($n = 9$)	0.036	
Lawton IADL (females)	6.4 (1.8) ($n = 50$)	6.4 (1.7) ($n = 37$)	6.5 (2.2) ($n = 13$)	0.729	
Diseases					
Hypertension (%)	68.7%	68.4%	69.6%	0.917	57.6%
Diabetes (%)	21.2%	26.3%	4.3%	0.017	12.1%
Sleep apnea syndrome (%)	23.2%	26.3%	13.0%	0.187	39.4%
Cerebrovascular disease (%)	6.1%	6.6%	4.3%	0.574	3.0%
Ischemic heart disease (%)	5.1%	3.9%	8.7%	0.329	9.1%
Chronic heart failure (%)	7.1%	6.6%	8.7%	0.515	6.1%
Parkinson (%)	4.0%	3.9%	4.3%	0.659	0.0%
Chronic pain (%)	13.1%	11.8%	17.4%	0.352	9.1%
Osteoporosis (%)	28.3%	23.7%	43.5%	0.065	17.2%
Hyperlipidemia (%)	36.4%	36.8%	34.8%	0.857	33.3%
Insomnia (%)	22.2%	23.7%	17.4%	0.525	18.2%
COPD, bronchial asthma (%)	10.1%	9.2%	13.0%	0.422	15.2%

The values represent the means (SD) where applicable. The comorbidities indicate the percentage of the patients who were treated for each disease. *P*-value was obtained by comparison between the interviewed and non-interviewed patients. COPD, chronic obstructive pulmonary disease; IADL, instrumental activities of daily living; GDS15, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

Table 2 Answer distribution in the interview-based survey and questionnaire-based survey

		Answer 1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	(Answers 4 and 5) per (answers 1 and 2)	*P*-value *vs* interview	*P*-value *vs* Q1
Interview ($n = 76$)	Q1	3 (3.9%)	9 (11.8%)	19 (25.0%)	18 (23.7%)	27 (35.5%)	3.75	–	–
	Q2	3 (3.9%)	6 (7.9%)	25 (32.9%)	19 (25.0%)	23 (30.3%)	4.67	–	0.655
	Q3	5 (6.6%)	2 (2.6%)	23 (30.3%)	19 (25.0%)	27 (35.5%)	6.57	–	0.277
Questionnaire ($n = 61$)	Q1	3 (4.9%)	1 (1.6%)	10 (16.4%)	18 (29.5%)	29 (47.5%)	11.75	0.054	–
	Q2	3 (4.9%)	7 (11.5%)	8 (13.1%)	18 (29.5%)	25 (41.0%)	4.30	0.872	0.100
	Q3	4 (6.6%)	4 (6.6%)	5 (8.2%)	17 (27.9%)	31 (50.8%)	6.00	0.870	0.292

Question 1 was "If it is necessary to live, would you like to start using a gastrostomy tube or a nasal tube?" Answer 1, "I definitely want to start"; answer 2, "If anything, I want to start"; answer 3, "I don't know"; answer 4, "If anything, I do not want to start"; and answer 5, "I definitely do not want to start." Question 2 was "If it is necessary to live, would you like to start intravenous hyperalimentation?" The five possible response options were the same as Question 1. Question 3 was "Do you believe it is acceptable to die as the result of undernutrition?" The five possible answers were: answer 1, "Definitely unacceptable"; answer 2, "If anything, I would consider it unacceptable";answer 3, "I don't know"; answer 4, "If anything, I would consider it acceptable"; and answer 5, "Definitely acceptable." (Answers 4 and 5) / (answers 1 and 2) was calculated by the number of the patients with answers 4 or 5 divided by the number of the patients with answers 1 or 2. *P*-values were obtained by comparing (answers 4 and 5) / (Answers 1 and 2) using the χ^2-test.

Table 3 Associations between the background factors and the answers about artificial nutrition and hydration

			Pro ANH	*P*-value	No ANH	*P*-value	Definitely, No ANH	*P*-value
			n (%)		*n* (%)		*n* (%)	
Sex	Male	*n* = 38	3 (7.9%)	0.307	15 (39.5%)	0.066	9 (23.7%)	0.602
	Female	*n* = 38	1 (2.6%)		23 (60.5%)		11 (28.9%)	
Age	≥80	*n* = 42	2 (4.8%)	0.609	23 (54.8%)	0.356	11 (26.2%)	0.978
	<80	*n* = 34	2 (5.9%)		15 (44.1%)		9 (26.5%)	
MMSE (cut-off 26/27)	≥27	*n* = 43	3 (7.0%)	0.414	22 (51.2%)	0.817	12 (27.9%)	0.719
	21–26	*n* = 33	1 (3.0%)		16 (48.5%)		8 (24.2%)	
MMSE (cut-off 23/24)	≥24	*n* = 71	4 (5.6%)	0.757	36 (50.7%)	0.500	19 (26.8%)	0.604
	21–23	*n* = 5	0 (0.0%)		2 (40.0%)		1 (20.0%)	
GDS (cut-off 9/10)	≥10	*n* = 6	0 (0.0%)	0.708	4 (66.7%)	0.446	2 (33.3%)	0.487
	≤9	*n* = 68	4 (5.9%)		33 (48.5%)		17 (25.0%)	
GDS (cut-off 4/5)	≥5	*n* = 36	3 (8.3%)	0.287	18 (50.0%)	1.000	10 (27.8%)	0.687
	≤4	*n* = 38	1 (2.6%)		19 (50.0%)		9 (23.7%)	
Barthel Index	100	*n* = 54	3 (5.6%)	0.706	25 (46.3%)	0.295	14 (25.9%)	0.935
	<100	*n* = 20	1 (5.0%)		12 (60.0%)		5 (25.0%)	
Lawton Index (male)	5	*n* = 27	2 (7.4%)	0.624	11 (40.7%)	0.635	7 (25.9%)	0.537
	≤4	*n* = 10	1 (10.0%)		4 (40.0%)		2 (20.0%)	
Lawton Index (female)	8	*n* = 15	1 (6.7%)	0.405	7 (46.7%)	0.191	3 (20.0%)	0.342
	≤7	*n* = 22	0 (0.0%)		15 (68.2%)		7 (31.8%)	

The χ^2-test or Fisher's exact test was carried out to compare the ratio of the answers regarding artificial nutrition and hydration (ANH) between the two groups. The *P*-values are shown. GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination.

scores of less than 24, percentage of GDS scores of 10 or more, and comorbidities of diabetes mellitus and osteoporosis differed between the interviewed and non-interviewed patients (Table 1). Subsequently, we carried out a multiple logistic regression analysis (forward selection method) using these factors as independent variables. As Lawton IADL scores showed collinearity with MMSE scores of 23 or less among males, we did not utilize the Lawton IADL score as an independent variable. Only MMSE scores of 23 or less and age showed a significant association with interview consent (OR 5.097, 95% CI 1.337–19.434; $P = 0.017$, and OR 1.105, 95% CI 1.005–1.214; $P = 0.038$, in order).

We also evaluated the association between the distribution of answers about ANH and various background factors (i.e. sex, age, MMSE, GDS, Barthel Index and Lawton IADL index). No factors significantly influenced the percentage of "Pro ANH," "No ANH" or "Definitely, No ANH" answers in the total obtained answers (Table 3). No background diseases showed any significant associations with the answers about ANH. In terms of MMSE scores, we applied cut-off points 26/27 and 23/24, because just five patients with MMSE scores of 23 or less could be interviewed. Likewise, cut-off points 4/5 and 9/10 for GDS scores were used, because just six patients with GDS scores of 10 or higher could be interviewed.

Percentage of the answers preserved in medical records

We found that 64 patients (84.2% of the interviewed patients) from the interview survey agreed to their responses being preserved in their medical records. Specifically, all of the four "Pro ANH" patients, and 35 of the 38 "No ANH" patients agreed to have their answers preserved in their medical records (92.9%), showing a significant difference from the patients who selected the option "I don't know" in some questions (71.0%; $P = 0.013$).

Of importance, we found that just 21 of the 76 interviewed patients (27.6%) had discussed ANH during end-of-life care with others. Furthermore, just 11 of the 20 "Definitely, No ANH" patients (55%) had discussed this topic with others. Likewise, just 18 of the 37 "No ANH" patients (48.6%) had previously discussed this topic.

Discussion

In the present study, we showed the percentage of elderly patients that were against ANH during end-of-life care. In our interview survey, 26.3% of the interviewed patients were definitely against ANH during end-of-life care. We speculate that these patients are already

prepared to make an advance directive if it is introduced. Consistent with previous surveys, the number of "Pro ANH" patients was very low,[9,17] and showed a serious gap from the actual prevalence of ANH in Japan.[5]

Importantly, our findings also showed that many elderly patients did not have clear wishes about their end-of-life care. Nearly half of the interviewed patients were included in the "Undecided" group. This high percentage in the "Undecided" group was partially explained by the simplified grouping of the three questions, namely, the patients who responded "I don't know" to one of the three questions were all included in the "Undecided" group. However, only approximately 30% of the patients in the interview survey responded "I don't know" to any of the questions, which is not a negligible number. Furthermore, only approximately 40% of the patients selected definite answers (i.e. answers 1 or 5) for any of the questions in the interview survey. It is important to encourage elderly patients to think about their own future end-of-life care, and at the same time, to create a method of a comprehensive decision-making process to be used for cases in which the wishes are not clearly expressed.

The comparison of the two survey methods suggested that the questionnaire-based survey obtained responses only from participants who had a clear idea of what they wanted, because the response rate for "I don't know" was significantly lower in the questionnaire-based survey than in the interview-based survey. The number of patients who wanted to start tube feeding was lower in the questionnaire-based survey than in the interview-based survey, although the difference was not statistically significant. A negative image of gastrostomy might have affected participants' responses in the questionnaire-based survey, as they did not have interviewers' explanations. The other answer distributions were almost similar between the two surveys.

Our findings also suggested that cognitive decline prevents patients from participating in discussion of these issues, although their reasons for rejection were not well determined. This result is reasonable, because dementia frequently involves passive behavior.[19] Although cognitive dysfunction does not necessarily imply an impossibility of self-determination, it would require more effort to ascertain the wishes of patients with dementia.[20]

At the same time, we could not find any factors that significantly influenced thoughts about ANH. This finding is rather important, suggesting that declining cognitive function or ADL, fluctuation of depressed mood, or old age would not substantially affect thoughts about ANH. This finding is consistent with a recent systematic review of longitudinal studies about end-of-life preferences.[21]

Many of the patients never discussed these issues with others. Thus, our investigation was the first to ascertain and preserve these wishes utilizing only simple interviews (approximately 20 min per patient). Importantly, most of the patients who expressed some wishes agreed to have their answers preserved in their medical records. Although real decision-making would still be complicated and difficult, these documents could have some effect on future end-of-life care decisions, even in the cases without strong wishes.[22] We speculate that our surveys showed a potentially novel method of advance care planning.

There are some limitations associated with the present study. First, the participants of our investigation were recruited from a single institution. In addition, a substantial number of inpatients had some uncontrolled anxiety or irritability, and were excluded from the survey. However, the similarity in the findings from the interview survey on inpatients and the questionnaire survey on outpatients would support the generalizability of our findings. Second, to clarify the association between dementia or depression and ANH preference, more subjects with MMSE scores of less than 24 or with GDS scores of more than 9 would be required. However, the cut-off point of less than 27 for the MMSE can be also utilized for screening mild cognitive impairment,[23] and the cut-off point of 5 or more on the GDS is frequently utilized for screening depressive state.[24] Thus, our findings support the notion that the presence of mild cognitive impairment or depressive state does not affect ANH preference. Third, we cannot know precisely, even through interviews, what the patients assumed from our explanations. This point would be most difficult to address in advance care planning for elderly patients.

In conclusion, our investigations showed the distributions of elderly patients' wishes regarding ANH during end-of-life care, when these are preserved in medical records, simulating an advance directive. Although the majority of the patients were against ANH, many elderly patients did not express definite wishes on this issue in Japan. In addition, our findings suggested that patients with cognitive impairment tended to avoid discussing these issues. However, we also found that the percentage of the wishes against ANH was not associated with the presence of mild cognitive impairment or depressive state.

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design. Dr Ishii and Dr Okamoto contributed to data collection. Dr K Yamaguchi and Dr Akishita contributed to the study design and review of the manuscript. Dr Iijima, Dr Ogawa and Dr Ouchi contributed to review of the manuscript.

Disclosure statement

No potential conflicts of interest were disclosed.

References

1 Japanese Geriatric Society Ethics Committee, Iijima S, Aida N *et al.* Position statement from the Japan Geriatrics Society 2012: end-of-life care for the elderly. *Geriatr Gerontol Int* 2014; **14**: 735–739.
2 Ikegami N, Ikezaki S. Nursing homes and end-of-life care in Japan. *J Am Med Dir Assoc* 2013; **14**: 718–723.
3 Mitchell SL, Teno JM, Kiely DK *et al.* The clinical course of advanced dementia. *N Engl J Med* 2009; **361**: 1529–1538.
4 Aita K, Takahashi M, Miyata H, Kai I, Finucane TE. Physicians' attitudes about artificial feeding in older patients with severe cognitive impairment in Japan: a qualitative study. *BMC Geriatr* 2007; **7**: 22.
5 Sako A, Yasunaga H, Horiguchi H *et al.* Prevalence and in-hospital mortality of gastrostomy and jejunostomy in Japan: a retrospective study with a national administrative database. *Gastrointest Endosc* 2014; **80**: 88–96.
6 Goldberg LS, Altman KW. The role of gastrostomy tube placement in advanced dementia with dysphagia: a critical review. *Clin Interv Aging* 2014; **9**: 1733–1739.
7 American Geriatrics Society Ethics Committee and Clinical Practice and Models of Care Committee. American Geriatrics Society feeding tubes in advanced dementia position statement. *J Am Geriatr Soc* 2014; **62**: 1590–1593.
8 Kuo S, Rhodes RL, Mitchell SL, Mor V, Teno JM. Natural history of feeding-tube use in nursing home residents with advanced dementia. *J Am Med Dir Assoc* 2009; **10**: 264–270.
9 Clarke G, Harrison K, Holland A, Kuhn I, Barclay S. How are treatment decisions made about artificial nutrition for individuals at risk of lacking capacity? A systematic literature review. *PLoS ONE* 2013; **8**: e61475.
10 Livingston G, Leavey G, Manela M *et al.* Making decisions for people with dementia who lack capacity: qualitative study of family carers in UK. *BMJ* 2010; **341**: c4184.
11 Monturo CA, Strumpf NE. Advance directives at end-of-life: nursing home resident preferences for artificial nutrition. *J Am Med Dir Assoc* 2007; **8**: 224–228.
12 Vandervoort A, Houttekier D, Vander Stichele R, van der Steen JT, Van den Block L. Quality of dying in nursing home residents dying with dementia: does advanced care planning matter? A nationwide postmortem study. *PLoS ONE* 2014; **9**: e91130.
13 Nakazawa K, Kizawa Y, Maeno T *et al.* Palliative care physicians' practices and attitudes regarding advance care planning in palliative care units in Japan: a nationwide survey. *Am J Hosp Palliat Care* 2014; **31**: 699–709.
14 Miyata H, Shiraishi H, Kai I. Survey of the general public's attitudes toward advance directives in Japan: how to respect patients' preferences. *BMC Med Ethics* 2006; **7**: E11.
15 van der Steen JT, van Soest-Poortvliet MC, Hallie-Heierman M *et al.* Factors associated with initiation of advance care planning in dementia: a systematic review. *J Alzheimers Dis* 2014; **40**: 743–757.
16 Komiya K, Ishii H, Teramoto S *et al.* Medical professionals' attitudes toward tube feeding for themselves or their families: a multicenter survey in Japan. *J Palliat Med* 2012; **15**: 561–566.
17 Schrader SL, Nelson ML, Eidsness LM. "South Dakota's dying to know": a statewide survey about end of life. *J Palliat Med* 2009; **12**: 695–705.
18 Kawasaki A, Matsushima M, Miura Y *et al.* Recognition of and intent to use gastrostomy or ventilator treatments in older patients with advanced dementia: differences between laypeople and healthcare professionals in Japan. *Geriatr Gerontol Int* 2015; **15**: 318–325.
19 Colling KB. A taxonomy of passive behaviors in people with Alzheimer's disease. *J Nurs Scholarsh* 2000; **32**: 239–244.
20 Poppe M, Burleigh S, Banerjee S. Qualitative evaluation of advanced care planning in early dementia (ACP-ED). *PLoS ONE* 2013; **8**: e60412.
21 Auriemma CL, Nguyen CA, Bronheim R *et al.* Stability of end-of-life preferences: a systematic review of the evidence. *JAMA Intern Med* 2014; **174**: 1085–1092.
22 Teno JM, Gruneir A, Schwartz Z, Nanda A, Wetle T. Association between advance directives and quality of end-of-life care: a national study. *J Am Geriatr Soc* 2007; **55**: 189–194.
23 Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009; **43**: 411–431.
24 Weintraub D, Oehlberg KA, Katz IR, Stern MB. Test characteristics of the 15-item geriatric depression scale and Hamilton depression rating scale in Parkinson disease. *Am J Geriatr Psychiatry* 2006; **14**: 169–175.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Answer combinations for the interview- and questionnaire-based surveys.
Appendix SI English translation of the questionnaire.
Appendix SII Explanatory document.

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Comparison of short-term mortality and morbidity between parenteral and enteral nutrition for adults without cancer: a propensity-matched analysis using a national inpatient database[1,2]

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Abstract

Background: Proper artificial nutrition for patients who are unable to eat normally is an ongoing, unresolved concern in geriatric medicine and home medical care. Controversy surrounds prognostic differences between parenteral and enteral nutrition, 2 methods for artificial nutrition.

Objectives: Short-term outcomes of parenteral and enteral nutrition for patients who are unable to eat normally were compared and analyzed.

Design: Data were acquired from patients selected from a national inpatient database covering 1057 hospitals in Japan. Participants had received artificial nutrition between April 2012 and March 2013, were aged ≥20 y, and did not have cancer. They were separated into 2 groups: those who received parenteral nutrition and those who received enteral nutrition. We performed one-to-one propensity score matching between the groups. The primary outcome measurements were mortality rates at 30 and 90 d after the start of the procedure. The secondary outcomes were postprocedural complications, pneumonia, and sepsis. We analyzed survival length of stay after the procedure with the use of a Cox proportional hazards model.

Results: There were 3750 patients in the parenteral group and 22,166 patients in the enteral group. Propensity score matching created 2912 pairs in the 2 groups. Patients with a similar propensity score (probability of being assigned to the enteral group) calculated from the baseline condition were matched. Mortality rates at 30 and 90 d after start of treatment were 7.6% and 5.7% ($P = 0.003$) and 12.3% and 9.9% ($P = 0.002$) in the parenteral and enteral groups, respectively. In Cox regression analysis, the HR for the enteral group relative to the parenteral group was 0.62 (95% CI: 0.54, 0.71; $P < 0.001$). The incidences of postprocedural pneumonia and sepsis were 11.9% and 15.5% ($P < 0.001$) and 4.4% and 3.7% ($P = 0.164$) for the parenteral and enteral groups, respectively.

Conclusion: The present analysis showed the better survival rate with enteral compared with parenteral nutrition for adults who were not suffering from cancer. This trial was registered at clinicaltrials.gov as NCT02512224.

Keywords:

elderly mortality morbidity parenteral nutrition enteral nutrition

INTRODUCTION

Artificial nutrition is an option in cases in which patients are unable to eat normally, although the indication for its use is not agreed on. There are 2 options for artificial nutrition: parenteral nutrition, also called intravenous feeding and often achieved by central venous port insertion, and enteral nutrition, in which nourishment is introduced directly into the stomach. Parenteral nutrition is considered to carry risks of catheter infection and suppression of intestinal immunity, and for this reason, enteral nutrition is thought to be superior to parenteral nutrition. The American Society for Parenteral and Enteral Nutrition recommends that enteral nutrition, if feasible, rather than parenteral nutrition should be used (1). In 2004 and 2010 it was estimated that enteral nutrition was used in at least 145,000 cases in the United States and at least 119,000 cases in

Japan (2), respectively.

However, enteral nutrition is not without risks. For example, 2 options for enteral nutrition, percutaneous endoscopic gastrostomy and percutaneous transesophageal gastrotubing, carry a risk of postprocedural aspiration pneumonia caused by gastroesophageal reflux. In addition, low survival rates after percutaneous endoscopic gastrostomy have been reported (2–8).

Only a few studies have compared mortality between parenteral and enteral nutrition in patients who need artificial nutrition. Home parenteral nutrition was shown to be a safe substitute for percutaneous endoscopic gastrostomy in patients with amyotrophic lateral sclerosis (9), and there was no difference in mortality between 546 elderly patients that could be attributed to type of artificial nutrition (10). In fact, there is one study in patients with traumatic brain injury in which patients who received parenteral nutrition had slightly lower mortality than did patients receiving enteral nutrition (11). These studies are limited, however, by small sample sizes and lack of statistical adjustment for patients' backgrounds. We conclude that, despite the prevailing view, the identification of the safest option for artificial nutrition deserves closer attention.

This study was undertaken to compare short-term outcomes between parenteral and enteral nutrition for patients who are unable to receive oral feeding. We adjusted for patient characteristics and used a national inpatient database in Japan.

METHODS

Setting and participants

For this study, we used the Japanese Diagnosis Procedure Combination database, the details of which were described elsewhere (12–14). The database includes administrative claims and discharge abstract data. In 2012, these data were collected for ~7 million inpatients from 1057 participating hospitals across Japan, which amounted to approximately half of the acute care hospitalizations in the country. The database includes the following information: unique hospital identifiers; patient's age and sex; main diagnoses, comorbidities on admission, and postadmission complications, both main diagnoses, comorbidities on admission, and postadmission complications are recorded with the International Classification of Diseases, 10th Revision (text data were also recorded in Japanese) (http://www.dis.h.u-tokyo.ac.jp/byomei/icd10/); procedures coded with original Japanese codes; drugs and devices used; and discharge status. All clinical data for each patient were recorded at discharge by the attending physicians. Physicians are required to record diagnoses consistent with guidelines in published standards, which optimizes accuracy and consistency among them. The dates of hospital admission, discharge, surgery, bedside procedures, and drugs administered were recorded in a uniform format.

All patient identifiers were removed from the database. Study approval was obtained from the Institutional Review Board of the University of Tokyo. Because of the anonymous nature of the data, the board waived the need for informed consent.

We selected patients aged ≥20 y who had undergone either parenteral nutrition by central venous port insertion or enteral nutrition by percutaneous endoscopic gastrostomy, percutaneous transesophageal gastrotubing, or ileostomy between 1 April 2012 and 31 March 2013. We excluded patients who had been diagnosed with cancer. Patients who received both gastrostomy and central venous port insertion were assigned to the gastrostomy group. Hospital volume was defined as the average annual number of patients who had undergone any of the artificial nutrition methods considered in this study at each hospital.

We identified 28 disease categories, which are listed in Table 1, accompanied by their codes from the International Classification of Diseases, 10th Revision. The type of disease may, in some cases, have influenced the type of artificial nutrition selected.

View this table:
In this window In a new window

TABLE 1

ICD-10 codes for the underlying diseases used for propensity score matching[1]

The database includes daily information on all the intravenous fluids and enteral nutrients prescribed for each patient. With the use of these data, we calculated the calorie and amino acid intake on the seventh day after the operation. The database includes data for body weight and height on admission for each patient. With the use of these data, we calculated the median (interquartile range) values for body

weight and height in each group.

Outcomes

The primary outcomes were defined as the rate of mortality at 14, 30, and 90 d after the start of the procedure. The secondary outcomes included the incidence of postprocedural pneumonia, sepsis occurring during hospitalization, or readmission within 30 d of discharge. For deceased patients, we compared comorbidities on admission and postprocedural complications between groups.

Statistical analysis

Propensity score matching was used for balancing the baseline characteristics between patients in the parenteral and enteral groups (15). Propensity score methods are a powerful tool for comparing groups with similar observed characteristics without specifying the relation between confounders and outcomes (13, 14, 16, 17). First, to determine the propensity score for each patient, logistic regression for predicting the probability that a patient would receive enteral nutrition rather than parenteral nutrition was modeled for the following potential confounders: age of patient, sex of patient, volume of the patient's hospital, whether the patient had been admitted on an emergency basis, and the underlying disease from the 28 categories. The 28 disease categories consisted of the following: 1) major cause of disabled feeding, 2) diseases that could cause intestinal failure and influence the assignment of enteral or parenteral feeding (i.e., bowel infection, inflammatory bowel disease, ileus, postoperative intestinal problems, gastrointestinal hemorrhage, ischemic intestinal disease, malabsorption, cholelithiasis and cholangitis, pancreatic disease, and chronic liver disease), and 3) other major diseases that may, in some cases, have influenced the type of artificial nutrition selected or prognosis of the patient. A receiver operating curve (ROC) was created to calculate the AUC (C-statistics) to evaluate goodness-of-fit. A one-to-one match with the use of nearest-neighbor matching was performed on the basis of the estimated propensity scores of each patient. A match occurred when one patient in the parenteral group had an estimated score within 0.2 SDs of another in the enteral group (18).

We examined the characteristics of all patients and of propensity-matched patients, and we used the standardized difference to compare the patient characteristics between the parenteral and enteral nutrition groups. The standardized difference compares the difference in means in units of the pooled SD. Each standardized difference was described as a percentage—that is, it was multiplied by 100 to obtain the shown values. The standardized difference for age was calculated from the difference in mean age. An absolute standardized difference >10% indicates a significant imbalance in a covariate (18–23).

For comparisons of 14-, 30-, and 90-d mortality rates after the start of the procedure; the 30-d readmission rate; the rate of postprocedural pneumonia; and the rate of postprocedural sepsis, we used chi-square tests between the parenteral and enteral groups in the propensity score-matched groups. Risk differences and their 95% CIs were calculated. In the chi-square test, log-rank test, and Cox regression analyses, we did not take into account the matched-pair nature. Instead, in the logistic regression analyses for the propensity score-matched patients, we used generalized estimating equations to account for clustering within propensity score-matched pairs of 2 patients for the parenteral and enteral groups (19, 24, 25).

We used the Kaplan-Meier method and log-rank test to compare short-term survival between the propensity-matched parenteral and enteral groups. Living discharged patients were regarded as censored cases. We performed a Cox regression analysis to estimate the HRs of death for the enteral nutrition group relative to the parenteral nutrition group. All statistical analyses were conducted by using IBM SPSS, version 22 (IBM SPSS).

RESULTS

Patients were selected from the database according to the criteria outlined above. There were 3750 patients who had received parenteral nutrition and 22,166 patients who had received enteral nutrition. In the enteral nutrition group, 21,665 patients had undergone gastrostomy, 133 patients had undergone percutaneous transesophageal gastrotubing, and 368 patients had undergone ileostomy. Propensity score matching created 2912 pairs in the parenteral and enteral nutrition groups. The AUC of the ROC analysis for goodness-of-fit of the model used for propensity score matching was 0.764 (95% CI: 0.755, 0.773; $P < 0.001$). The value of 0.764 indicated a fair level of fit. Table 2 shows the baseline characteristics of the unmatched parenteral and enteral groups ($n = 25,916$) and of the propensity score-matched groups ($n = 5824$). In the unmatched groups, patients who were elderly, admitted on an emergency basis, or had pneumonia, intracranial injury, cerebrovascular disease, neuromuscular disease, or dementia were more likely to receive enteral nutrition than parenteral nutrition. Patients with