interval between the onset and surgery have been considered to be the critical factors determining the qualitative postoperative recovery.[12] Incomplete deficits, compared to complete deficits, should be associated with better outcomes. Indeed, the one-year complete recovery rate has been demonstrated to be approximately 89% for patients with incomplete deficits, but only 37.5% for those with complete deficits,[11] and similar trends have been demonstrated numerous times in the literature.[12,38] In addition, it is necessary to focus on the timing of surgery. In patients with a complete deficit, it has been shown in an analysis of 35 patients with SSEH that a good neurological recovery can be achieved after prompt surgery when the time interval from initial ictus to surgery is less than 48 hours, and when the duration of the complete neurological deficits is less than 12 hours.[11] Another study has demonstrated that a significantly better outcome was obtained if surgical decompression was carried out within 36 hours in patients with complete sensorimotor loss, and within 48 hours in those with incomplete deficits.[12] In a series of 14 patients reported by Shin et al, the patients who were surgically managed within 12 hours after the onset of symptoms scored significantly higher (84%) on the recovery scale of the Japanese Orthopedic Association[39] than those who underwent an operation from 12 to 24 hours after the initial attack (63.6%) and those who underwent surgery more than 24 hours after onset (46.7%).[38] Similar trends were also noted by Lawton et al.[37] The postoperative mortality rate of SSEH can thus be expected to range from around 3% to 6%.[11,37]

On the other hand, conservative management may still be an important treatment option in some subsets of SSEH patients with mild, rapid and spontaneously recovering neurological deficits.[8,40] Groen et al recently demonstrated that 84% of patients with SSEH treated non-surgically recovered completely.[8] However, this finding should be evaluated carefully in terms of the severity of the neurological deficits manifested by the subjects in their study. Indeed, as they stated, the subjects managed conservatively had less severe signs and symptoms and were more likely to be diagnosed based on an imaging modality alone, compared to the surgically-treated cases reported in the literature.[8] Moreover, a concurrent high surgical risk, such as bleeding diathesis, may also be a determinant in the decision for conservative management.[8] It is not surprising that some patients with minimal neurological signs may respond successfully to conservative management; however, the presence of cases in which an initial recovery was followed by deterioration requiring surgery should be kept in mind, and thus, the close observation of such patients should be carried out in a hospital with a neurosurgical specialty team.[40]

Perspectives

In the ordinary clinical setting, acute stroke patients almost never contact a neurologist initially, since most communities do not have an academic medical center with a systemic neurological assessment program.[41] It is known, however, that neurological complications contribute to morbidity and mortality in a wide range of patients,[42–44] and an accurate recognition of the condition is required to ensure prompt transfer to an appropriate treatment unit. Moreover, there is a limited time window for the administration of a thrombolytic agent, which is the only available medical treatment for acute ischemic stroke that has been proven to be effective.[45] In this regard, not only emergency medical services and emergency room departments, but also primary care physicians, should be familiar with the wide range of neurological problems that can develop in order to assure the optimal management of patients. We feel that an early and accurate diagnosis, as well as awareness of SSEH, remains a challenge for physicians, despite the accumulation of studies disclosing the nature of the disease. The current concise review emphasizes the pitfalls of evaluating patients with acute hemiparesis due to SSEH. The imaging analyses routinely applied for patients with acute cerebral ischemia do not rule out spinal bleeding, while the higher a cervical SSEH extends, the more likely it is to be seen on non-contrast computed tomographic scans.[4] The sudden onset of neck and/or back pain and progression of hemiparesis to paraplegia or tetraplegia during the observation period are clues leading to a timely diagnosis of cervical spinal lesions.[4,19,24,27,30–32] Although there may be limited access to MRI,[46] negative brain MRI findings, which strongly suggest the absence of ischemic cerebrovascular events,[47] may be an alternative trail turning the attention towards other regions, including the cervical spine. In addition, the presence of concurrent Broun-Séquard syndrome, characterized by the ipsilateral loss of proprioceptive sensitivity with the contralateral loss of pain and temperature sensitivity, can help to promptly diagnose the disease,[4,48–51] although this syndrome is not necessarily associated with hemiparesis as an initial neurological presentation.[52]

Stroke mimics may account for 20 to 25% of suspected stroke presentations,[53] and there are various conditions (Table 2) that have been demonstrated to act as stroke mimics in previous studies.[54–57] There are some discrepancies in the distribution of diagnoses, depending on the context, while seizure seems to be one of the major common denominators, being present in approximately 15 to 20% of the stroke mimic cases.[54–57] Some studies included the presence of cervical or spinal lesions in the conditions that mimicked stroke;[54,56] however, the lack of information regarding the disease spectrum precludes us from determining the actual frequency of SSEH among subjects with a condition mimicking stroke. Nevertheless, we believe that SSEH, especially in the cervical region, should also be included as such a clinical entity,[4] thereby leading to a high index of suspicion, prompt recognition and immediate intervention, which is essential to reduce or prevent major morbidity of the disease.[36] Several studies have demonstrated the safety of thrombolytic treatment in some subjects with stroke mimics,[58] although there has been

Table 2. The previously reported conditions that mimicked stroke.

Seizure
Systemic infection/sepsis
Brain tumor
Toxic/metabolic
Vestibular dysfunction
Syncope
Subdural hematoma
Subarachnoid hemorrhage
Intracranial hemorrhage
Transient global amnesia
Dementia
Conversion disorder
Migraine
Peripheral neuropathy

only a single report regarding a patient with SSEH mimicking a stroke being administered a thrombolytic agent as an initial treatment, and this was followed by urgent laminectomy without any bleeding complications.[29] Considering the narrow window for thrombolytic treatment in cases of ischemic stroke and the rarity of SSEH, one may argue that our proposal is not necessarily justified. On the other hand, the association between the administration of a thrombolytic agent and the secondary development of spinal epidural hematoma has been demonstrated anecdotally.[59,60] Moreover, the inappropriate administration of agents used for restoring cerebral blood flow may preclude prompt surgery for SSEH, due to the patient's modified hemostatic nature, although the information currently available may not necessarily support this concept.[29] Thus, we believe that it is necessary to take a proactive approach by adding SSEH to the list of differential diagnoses of ischemic stroke before fatal outcomes accumulate.[36] Finally, it should be kept in mind that we are always facing, as do most physicians at various times, diagnostic and therapeutic dilemmas, and carefully weighing all of the options and potential outcomes on a case-by-case basis is therefore essential.

Author Contributions

TA and TY drafted the manuscript and made equal contributions to the literature survey. SS, YA, and DN provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document. All authors have read and approved the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

REFERENCES

1. Aminoff MJ. Weakness and Paralysis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J (eds.) Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw Hill, 2012:181–6.
2. Groen RJ, Ponssen H. The spontaneous spinal epidural hematoma. A study of the etiology. *J Neurol Sci.* 1990;98(2–3):121–38.
3. Alexiadou-Rudolf C, Ernestus RI, Nanassis K, Lanfermann H, Klug N. Acute nontraumatic spinal epidural hematomas: An important differential diagnosis in spinal emergencies. *Spine.* 1998;23:1810–3.
4. Schmidley JW, Mallenbaum S, Broyles K. Spinal epidural hematoma: an important stroke mimic. *Acute Med.* 2013;12(1):36–9.
5. Jackson R. Case of spinal apoplexy. *Lancet.* 1869;2:5–6.
6. Bain W. A Case of Haematorrachis. *Br Med J.* 1897;2:455.
7. Kreppel D, Antoniadis G, Seeling W. Spinal hematoma: a literature survey with meta-analysis of 613 patients. *Neurosurg Rev.* 2003;26(1):1–49.
8. Groen RJ. Non-operative treatment of spontaneous spinal epidural hematomas: a review of the literature and a comparison with operative cases. *Acta Neurochir (Wien).* 2004;146(2):103–10.
9. Holtås S, Heiling M, Lönntoft M. Spontaneous spinal epidural hematoma: findings at MR imaging and clinical correlation. *Radiology.* 1996;199(2): 409–13.
10. Noth I, Hutter JJ, Meltzer PS, Damiano ML, Carter LP. Spinal epidural hematoma in a hemophilic infant. *Am J Pediatr Hematol Oncol.* 1993;15(1):131–4.
11. Liao CC, Lee ST, Hsu WC, Chen LR, Lui TN, Lee SC. Experience in the surgical management of spontaneous spinal epidural hematoma. *J Neurosurg.* 2004;100(1 Suppl Spine):38–45.
12. Groen RJ, van Alphen HA. Operative treatment of spontaneous spinal epidural hematomas: a study of the factors determining postoperative outcome. *Neurosurgery.* 1996;39(3):494–508.
13. Liu Z, Jiao Q, Xu J, Wang X, Li S, You C. Spontaneous spinal epidural hematoma: analysis of 23 cases. *Surg Neurol.* 2008;69:253–60.
14. Lobitz B, Grate I. Acute epidural hematoma of the cervical spine: an unusual cause of neck pain. *South Med J.* 1995;88:580–2.
15. Thiele RH, Hage ZA, Surdell DL, Ondra SL, Batjer HH, Bendok BR. Spontaneous spinal epidural hematoma of unknown etiology: case report and literature review. *Neurocrit Care.* 2008;9(2):242–6.
16. Gopalkrishnan CV, Dhakoji A, Nair S. Spontaneous cervical epidural hematoma of idiopathic etiology: case report and review of literature. *J Spinal Cord Med.* 2012;35(2):113–7.
17. Lowrey JJ. Spinal epidural hematomas. Experiences with three patients. *J Neurosurg.* 1959;16:508–13.
18. Beatty RM, Winston KR. Spontaneous cervical epidural hematoma. A consideration of etiology. *J Neurosurg.* 1984;61(1):143–8.
19. Marinella MA, Barsan WG. Spontaneously resolving cervical epidural hematoma presenting with hemiparesis. *Ann Emerg Med.* 1996;27(4):514–7.
20. Anderson TJ, Donaldson IM. Spontaneous resolution of cervical spinal epidural haematoma. *Postgrad Med J.* 1989;65:488–90.
21. Rothfus WE, Chedid MK, Deeb ZL, Abla AA, Maroon JC, Sherman RL. MR imaging in the diagnosis of spontaneous spinal epidural hematomas. *J Comput Assist Tomogr.* 1987;11(5):851–4.
22. Jamjoom ZA. Acute spontaneous spinal epidural hematoma: the influence of magnetic resonance imaging on diagnosis and treatment. *Surg Neurol.* 1996;46(4):345–9.
23. Sakamoto N, Yanaka K, Matsumaru Y, Nose T. Cervical epidural hematoma causing hemiparesis. *Arch Neurol.* 2003;60(5):783.
24. Lin IY. Diagnostic pitfall: nontraumatic spinal epidural hematoma mimicking a brainstem stroke. *Ann Emerg Med.* 2004;44(2):183–4.
25. Hsieh CF, Lin HJ, Chen KT, Foo NP, Te AL. Acute spontaneous cervical spinal epidural hematoma with hemiparesis as the initial presentation. *Eur J Emerg Med.* 2006;13(1):36–8.
26. Ishikawa E, Saito A, Kujiraoka Y, Matsumura A. Recovery of increased signal intensity of the cervical cord on magnetic resonance imaging after surgery for spontaneous spinal epidural hematoma causing hemiparesis. *Neurol India.* 2008;56(1):98–100.
27. Wang CC, Chang CH, Lin HJ, Lin KC, Kuo JR. Misdiagnosis of spontaneous cervical epidural haemorrhage. *Eur Spine J.* 2009;18(Suppl 2):210–2.
28. Nakanishi K, Nakano N, Uchiyama T, Kato A. Hemiparesis caused by cervical spontaneous spinal epidural hematoma: a report of 3 cases. *Adv Orthop.* 2011;2011:516382.
29. Son S, Kang DH, Choi DS, Kim SK, Lim BH, Choi NC. A case of spontaneous spinal epidural hematoma mimicking a stroke. *Neurologist.* 2012;18(1):41–3.

30. Shima H, Yasuda M, Nomura M, et al. A spinal epidural hematoma with symptoms mimicking cerebral stroke. *Nagoya J Med Sci.* 2012;74(1–2):207–10.
31. Matsumoto H, Miki T, Miyaji Y, et al. Spontaneous spinal epidural hematoma with hemiparesis mimicking acute cerebral infarction: two case reports. *J Spinal Cord Med.* 2012;35(4):262–6.
32. Liou KC, Chen LA, Lin YJ. Cervical spinal epidural hematoma mimics acute ischemic stroke. *Am J Emerg Med.* 2012;30(7):1322.e1–3.
33. Lemmens R, Ceuppens J, Wilms G, Depreitere B. Transient hemiparesis caused by spontaneous cervical epidural hematoma. *Acta Neurol Belg.* 2012;112(3):291–3.
34. Förster A, Griebe M, Wolf ME, Szabo K, Hennerici MG, Kern R. How to identify stroke mimics in patients eligible for intravenous thrombolysis? *J Neurol.* 2012;259(7):1347–53.
35. Sarikaya H, Yilmaz M, Luft AR, Gantenbein AR. Different pattern of clinical deficits in stroke mimics treated with intravenous thrombolysis. *Eur Neurol.* 2012;68(6):344–9.
36. Phookan G, Lehman RA, Kuhlengel KR. Cervical spinal epidural haematoma: the double jeopardy. *Ann Med.* 1996;28(5):407–11.
37. Lawton MT, Porter RW, Heiserman JE, Jacobowitz R, Sonntag VK, Dickman CA. Surgical management of spinal epidural hematoma: relationship between surgical timing and neurological outcome. *J Neurosurg.* 1995; 83(1):1–7.
38. Shin JJ, Kuh SU, Cho YE. Surgical management of spontaneous spinal epidural hematoma. *Eur Spine J.* 2006;15(6):998–1004.
39. Hirabayashi K, Miyakawa J, Satomi K, Maruyama T, Wakano K. Operative results and postoperative progression of ossification among patients with ossification of cervical posterior longitudinal ligament. *Spine* (Phila Pa 1976). 1981;6(4):354–64.
40. Duffill J, Sparrow OC, Millar J, Barker CS. Can spontaneous spinal epidural haematoma be managed safely without operation? A report of four cases. *J Neurol Neurosurg Psychiatry.* 2000;69(6):816–9.
41. Morgenstern LB, Lisabeth LD, Mecozzi AC, et al. A population-based study of acute stroke and TIA diagnosis. *Neurology.* 2004;62(6):895–900.
42. Brouns R, De Deyn PP. Neurological complications in renal failure: a review. *Clin Neurol Neurosurg.* 2004;107:1–16.
43. García-Cabrera E, Fernández-Hidalgo N, Almirante B, et al; Group for the Study of Cardiovascular Infections of the Andalusian Society of Infectious Diseases; Spanish Network for Research in Infectious Diseases. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation.* 2013;127(23):2272–84.
44. Inzitari M, Pozzi C, Ferrucci L, et al. Subtle neurological abnormalities as risk factors for cognitive and functional decline, cerebrovascular events, and mortality in older community-dwelling adults. *Arch Intern Med.* 2008;168(12): 1270–6.
45. Hacke W, Kaste M, Bluhmki E, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359(13):1317–29.
46. Emery DJ, Forster AJ, Shojania KG, Magnan S, Tubman M, Feasby TE. Management of MRI wait lists in Canada. *Health Policy.* 2009;4(3):76–86.
47. van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LM, Mali WP. Diffusion-weighted magnetic resonance imaging in acute stroke. *Stroke.* 1998;29(9):1783–90.
48. Hancock JB, Field EM, Gadam R. Spinal epidural hematoma progressing to Brown-Sequard syndrome: report of a case. *J Emerg Med.* 1997;15(3):309–12.
49. Adamson DC, Bulsara K, Bronec PR. Spontaneous cervical epidural hematoma: case report and literature review. *Surg Neurol.* 2004;62(2):156–9; discussion 159–60.
50. D'Souza M, Gass A, Lyrer P, Ott HW, Baumann T. Intravenous thrombosis cancelled in acute right hemiparesis. *Cerebrovasc Dis.* 2008;26(6):665–6.
51. Panciani PP, Forgnone S, Fontanella M, Ducati A, Lanotte M. Unusual presentation of a spontaneous spinal epidural haematoma. *Acta Neurol Belg.* 2009;109(2):146–8.
52. Cai HX, Liu C, Zhang JF, Wan SL, Uchida K, Fan SW. Spontaneous epidural hematoma of thoracic spine presenting as Brown-Séquard syndrome: report of a case with review of the literature. *J Spinal Cord Med.* 2011;34(4):432–6.
53. Fernandes PM, Whiteley WN, Hart SR, Al-Shahi Salman R. Strokes: mimics and chameleons. *Pract Neurol.* 2013;13(1):21–8.
54. Libman RB, Wirkowski E, Alvir J, Rao TH. Conditions that mimic stroke in the emergency department. Implications for acute stroke trials. *Arch Neurol.* 1995;52(11):1119–22.
55. Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. *Stroke.* 2003;34(1):71–6.
56. Hand PJ, Kwan J, Lindley RI, Dennis MS, Wardlaw JM. Distinguishing between stroke and mimic at the bedside: the brain attack study. *Stroke.* 2006;37(3):769–75.
57. Hemmen TM, Meyer BC, McClean TL, Lyden PD. Identification of nonischemic stroke mimics among 411 code strokes at the University of California, San Diego, Stroke Center. *J Stroke Cerebrovasc Dis.* 2008;17(1):23–5.
58. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. *Neurology.* 2010;74(17): 1340–5.
59. Clark MA, Paradis NA. Spinal epidural hematoma complicating thrombolytic therapy with tissue plasminogen activator—a case report. *J Emerg Med.* 2002;23(3):247–51.
60. Yeo LL, Lim JS, Sharma VK. Spinal epidural hematoma after intravenous thrombolysis for acute ischemic stroke. *J Neurol Sci.* 2009;284(1–2):190–1.

INTERNAL MEDICINE

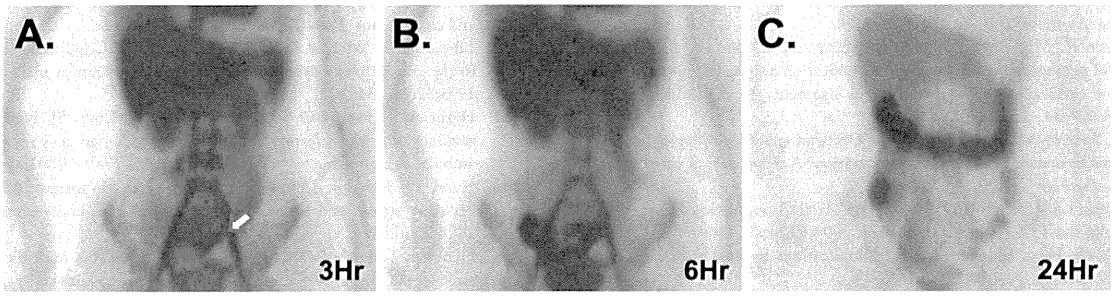
□ PICTURES IN CLINICAL MEDICINE □

Hypoalbuminemia and Technetium-99m-labeled Human Serum Albumin Scintigraphy

Tetsu Akimoto, Osamu Saito, Eiji Kusano and Daisuke Nagata

Key words: nephrotic syndrome, hypoalbuminemia, protein-losing enteropathy, human serum albumin scintigraphy

(Intern Med 53: 1723, 2014)
(DOI: 10.2169/internalmedicine.53.2538)



Picture.

A 17-year-old woman was admitted with a history of progressive swelling of the legs and shortness of breath with bilateral pleural effusion, mimicking nephrotic syndrome. Her serum albumin level was 1.7 g/dL despite negative urine protein. Technetium-99m-labeled human serum albumin (^{99m}Tc HSA) scintigraphy disclosed the accumulation of radioactivity (arrow) in the lower stomach three hours after injection (Picture A). The leaked ^{99m}Tc HSA moved into the ileum (Picture B) and transverse colon (Picture C), as shown on serial scintigrams, thus confirming the diagnosis of protein-losing enteropathy (PLE). A further workup demonstrated a disturbance in lymphatic perfusion mediated by lymphangioma.

Making an early diagnosis of PLE remains a challenge for physicians despite the accumulation of literature on this disorder (1). However, performing serial ^{99m}Tc HSA scanning over a 24-hour period should help to identify the responsible site and make a diagnosis of PLE with both high sensitivity and specificity (1, 2).

The authors state that they have no Conflict of Interest (COI).

References

1. Chau TN, Mok MY, Chan EY, et al. Evaluation of performance of measurement of faecal α(1)-antitrypsin clearance and technetium-99m human serum albumin scintigraphy in protein-losing enteropathy. Digestion **84**: 199-206, 2011.
2. Chiu NT, Lee BF, Hwang SJ, Chang JM, Liu GC, Yu HS. Protein-losing enteropathy: diagnosis with (99m)Tc-labeled human serum albumin scintigraphy. Radiology **219**: 86-90, 2001.

Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Japan
Received for publication January 22, 2014; Accepted for publication February 17, 2014
Correspondence to Dr. Tetsu Akimoto, tetsu-a@jichi.ac.jp
 Journal Website: http://www.naika.or.jp/imonline/index.html

Libertas Academica
FREEDOM TO RESEARCH

Open Access: Full open access to this and thousands of other papers at http://www.la-press.com.

Clinical Medicine Insights: Case Reports

Do We Have to Perform a Renal Biopsy? Clinical Dilemmas in a Case with Nephrotic Syndrome

Tetsu Akimoto, Naoko Otani, Eri Takeshima, Osamu Saito, Eiji Kusano and Daisuke Nagata

Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan.

ABSTRACT: Renal biopsy is one of the pivotal diagnostic tools used in the field of nephrology. A morphological analysis of the kidney may also be of value for the overall management of patients with diabetic nephropathy. However, the indications for renal biopsy differ considerably among nephrologists, and no global consensus regarding performing this procedure among diabetic patients with various renal manifestations has yet been achieved. In this report, we would like to describe our serendipitous experience with a male type 2 diabetic patient presenting with nephrotic syndrome complicated by concurrent gastric carcinoma. We also discuss several conundrums that arose in the current case, which had an impact on our diagnostic and therapeutic decisions.

KEYWORDS: diabetic nephropathy, nephrotic syndrome, paraneoplastic glomerular injury, membranous nephropathy, renal biopsy

CITATION: Akimoto et al. Do We Have to Perform a Renal Biopsy? Clinical Dilemmas in a Case with Nephrotic Syndrome. *Clinical Medicine Insights: Case Reports* 2014:7 67–70 doi: 10.4137/CCRep.S16312.

RECEIVED: April 21, 2014. **RESUBMITTED:** June 3, 2014. **ACCEPTED FOR PUBLICATION:** June 4, 2014.

ACADEMIC EDITOR: Athavale Nandkishor, Associate Editor

TYPE: Case Report

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: tetsu-a@jichi.ac.jp

This paper was subject to independent, expert peer review by a minimum of two blind peer reviewers. All editorial decisions were made by the independent academic editor. All authors have provided signed confirmation of their compliance with ethical and legal obligations including (but not limited to) use of any copyrighted material, compliance with ICMJE authorship and competing interests disclosure guidelines and, where applicable, compliance with legal and ethical guidelines on human and animal research participants.

Introduction

Renal biopsy is one of the pivotal diagnostic tools used in the field of nephrology. There are numerous diseases that can cause nephrotic syndrome, nephritic syndrome, and acute kidney injury, which have vastly different prognostic and therapeutic implications, illustrating the importance of histopathological examinations in the differential diagnosis.[1] However, the indications for renal biopsy differ considerably among nephrologists, and a global consensus regarding performing this procedure is lacking.[2] In this report, we describe our serendipitous experience with a male type 2 diabetic patient presenting with nephrotic syndrome complicated by concurrent gastric carcinoma. We also discuss several conundrums that arose in the current case, which had an impact on our diagnostic and therapeutic decisions.

Case Report

A 64-year-old male was referred to our unit with complaints of progressive swelling of his legs and weight gain of approximately 5 kg. Thirteen years before, he was found to have type 2 diabetes. Thereafter, he had received combination treatment with oral voglibose and nateglinide, which had kept his HbA1c levels between 6 and 7%. His serum creatinine (sCr) levels had increased gradually during the last two years. He had noticed the symptoms about three months before the referral, when his level of blood sCr was 1.7 mg/dL. He denied the use of any drugs, and his medical histories included hypertension and hyperlipidemia for more than 10 years.

His physical examination at the referral was unremarkable except for periorbital and leg edema. The laboratory data obtained on admission are summarized in Table 1. Tests for hepatitis B virus surface antigens and antibodies to the hepatitis C virus were negative. Renal sonography showed that the renal dimensions of the right kidney measured 113 × 60 mm, while those of the left kidney measured 115 × 66 mm, and the degree of renal cortex echogenicity was normal. The patient's urine was 3+ for protein and contained 8.9 g of protein in a 24 hour specimen. His proteinuria selectivity index

and creatinine clearance were 0.325 and 78.8 mL/minute, respectively. An ophthalmologic analysis revealed the patient to have simple diabetic retinopathy. On the other hand, the latex-agglutination test for fecal occult blood was positive (124 ng/mL) despite the absence of remarkable findings in the diagnostic thoracoabdominal computed tomography scan, and thus, endoscopic analyses of the upper and lower gastrointestinal tracts were performed. The presence of sigmoid colon polyps, which consisted of adenomatous tissue, was confirmed, while the gastric biopsy specimens revealed the presence of a well-differentiated adenocarcinoma confined to the submucosa. Endoscopic mucosal resection (EMR) was finally performed three months after the referral, confirming that the neoplastic tissue was of type 0–IIc based on the Paris endoscopic classification of superficial neoplastic lesions,[3] with a well-differentiated adenocarcinoma (Fig. 1), 7 × 6 mm in size. Eight months after the EMR, he was negative at occult fecal blood test but continued to exhibit nephrotic syndrome with a urine protein level of 3.69 g/g · Cr, an sAlb of 2.7 g/dL, and an sCr level of 2.04 mg/dL, and he was thus subjected to a pathological evaluation.

Table 1. Laboratory data on admission.

White blood cells	9400/μl	(3900–9800)
Hb	11.3 g/dl	(13.5–17.6)
Platelet count	25.3 × 10^4/μl	(13.0–36.9)
Fibrinogen	716 mg/dl	(129–271)
D-dimer	2.2 μg/ml	(0–1.5)
Blood urea nitrogen	31 mg/dl	(8–20)
Creatinine	1.8 mg/dl	(0.63–1.03)
Total protein	5.9 g/dl	(6.9–8.4)
Albumin	2.6 g/dl	(3.9–5.1)
Sodium	142 mmol/l	(136–148)
Potassium	5.7 mmol/l	(3.6–5.0)
Chloride	110 mmol/l	(96–108)
Calcium	8.8 mg/dl	(8.8–10.1)
Phosphorus	4.0 mg/dl	(2.4–4.6)
Asparate aminotransferase	15 IU/l	(11–30)
Alanine aminotransferase	13 IU/l	(4–30)
C-reactive protein	0.24 mg/dl	(0–0.14)
IgG	856 mg/dl	(870–1700)
IgA	276 mg/dl	(110–410)
IgM	94 mg/dl	(33–160)
CEA	1.0 ng/ml	(<5)
CA19–9	8 U/ml	(<37)
FBS	151 mg/dl	(70–109)
HbA1c	6.70%	(4.3–5.8)

Note: The reference ranges for each parameter used at our institute are indicated in the brackets.
Abbreviations: Hb, hemoglobin; Ig, immunoglobulin; CEA, carcinoembryonic antigen; CA, carbohydrate antigen; FBS, fasting blood sugar.

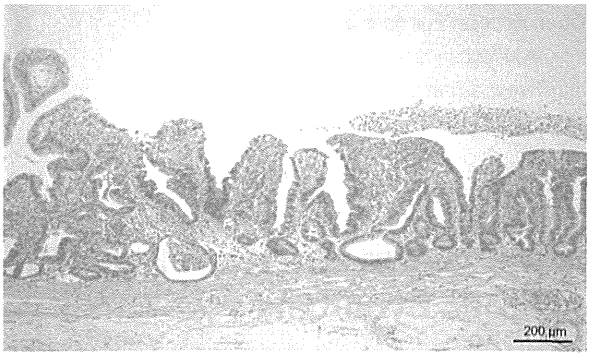


Figure 1. A photomicrograph of the EMR specimen. A type 0–IIc lesion with a well-differentiated adenocarcinoma with negative lymphovascular involvement was found (hematoxylin and eosin stain). The scale bar is indicated.

The renal biopsy consisted of three cores of renal parenchyma with 32 glomeruli, almost half of which were globally sclerotic. There were glomeruli with hyalinotic lesions, globally widened mesangial regions, and a number of rounded acellular mesangial nodules; and also interstitial infiltration of lymphocytes, atrophic changes in the tubule structure, interstitial fibrosis, and arteriolar hyalinization were identified (Fig. 2). Immunofluorescence staining failed to demonstrate the linear staining of IgG along the glomerular capillary wall. Instead, the presence of focal deposits of IgM in the depending portions of the areas of hyalinosis was confirmed. Electron microscopy failed to show the presence of electron-dense deposits on the subepithelium of the glomerular basement membrane, which is a suggestive finding of membranous nephropathy.[4]

Based on the renal pathological findings, combined with the patient's clinical pictures, he was finally diagnosed to have nephrotic syndrome due to diabetic nephropathy, and treatment with olmesartan medoxomil at 20 mg/day, amlodipine besilate at 5 mg/day, and furosemide at 80 mg/day, which had been started after the referral, as well as the oral hypoglycemic agents described above, was continued. Despite the absence of any exacerbation of the blood pressure control, his renal function gradually declined and a periodic hemodialysis program finally commenced 21 months after the renal biopsy.

Discussion

Performing a renal biopsy for proteinuric diabetics has usually been considered when the presence of a renal disease other than diabetic nephropathy is suggested by clinical signs, such as rapid deterioration of the renal function, microscopic or macroscopic hematuria, and proteinuria in newly diagnosed diabetics without retinopathy or neuropathy.[5–7] On the other hand, the association of chronic renal insufficiency, nephrotic syndrome, and diabetes with microangiopathic complications such as retinopathy makes a diagnosis of diabetic nephropathy probable, diminishing the need for a renal biopsy.[5,8,9] However, several recent studies have suggested a morphological analysis

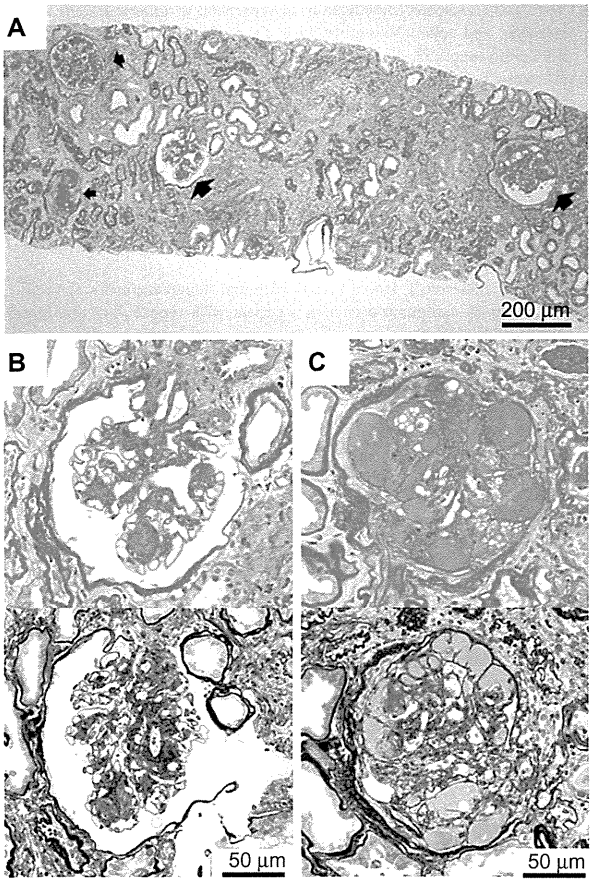


Figure 2. The renal biopsy findings. (**A**) A low power view showing the diffuse distribution of glomeruli with various stages of diabetic glomerular injuries, including glomeruli with hyalinotic lesions (narrow arrow), a moderate increase in mesangial matrix and thickening of the capillary wall (medium arrow), as well as nodule formation (wide arrows) (periodic acid-Schiff stain). Two sections of the same glomerulus with nodular lesions (**B**) and enormous exudative lesions with some bubbles, probably representing plasma proteins/lipids (**C**) (upper panel, periodic acid-Schiff stain; lower panel, periodic acid methenamine silver-Masson trichrome stain). The scale bar is indicated in each panel.

of the kidney to be of value for the overall management of patients with diabetic nephropathy,[5–10] implying the diagnostic potential of such a procedure in the overall assessment for diabetics with various renal manifestations. Considering the clinical picture of our patient at the referral, one might have straightforwardly attributed the nephrotic syndrome to diabetic nephropathy without pathological confirmation, and might even argue that the patient's renal pathological findings were not surprising. However, the clinical significance of the current case should be considered carefully in terms of the fact that the concurrent gastric carcinoma was found before arriving at the conclusion that the nephrotic syndrome was etiologically linked to diabetic glomerular injuries.

Nephrotic syndrome has been a focus of studies as one of the pivotal manifestations of the glomerular damage associated with various kinds of neoplasms,[11–13] while membranous nephropathy, one of the most common causes of adult nephrotic syndrome worldwide,[14] is the most common paraneoplastic glomerulopathy associated with solid tumors.[11–13] The main problem is to determine how thorough the search for neoplasia should be in such nephrotic subjects. Experts recommend performing basic routine cancer screening procedures, including chest radiography, an occult blood survey of stool specimens, colonoscopy, and measurements of the carcinoembryonic antigen (CEA) and prostate-specific antigen levels, especially in older patients with newly diagnosed membranous nephropathy without any other obvious causes. In addition, further investigations, such as bronchoscopy, gastroscopy, and CT, may be in order after the first-line assessment.[11,13] However, although some of these examinations may be carried out in the ordinary clinical setting,[7,15] the extent of the workup depends on the judgment of the primary physician. On the other hand, the validity of such a policy among the nephrotic patients whose renal pathological diagnoses are lacking or those with glomerulopathy other than membranous nephropathy remains to be established. We believe, however, that there are some subsets of nephrotic patients who would benefit from the screening for malignancies, as described in the current report. Otherwise, we might have overlooked the concurrent gastric carcinoma in the present case if we had simply ascribed the nephrotic syndrome to diabetic nephropathy regardless of the presence or absence of the pathological confirmation and had failed to perform upper gastrointestinal endoscopy, which led us to promptly identify the disease.

Fecal immunochemical tests are recommended as the first-choice modality for colorectal cancer screening in average-risk populations,[16] although the current evidence is insufficient to recommend for or against routine surveys to detect gastric or esophageal carcinoma in patients with characteristics similar to those of our patient, ie, positivity for fecal occult blood with negativity on colonoscopy, based on a population-based colorectal cancer screening program.[17] Nevertheless, it has been shown that performing upper gastrointestinal endoscopy in patients with a positive fecal occult blood test alone is not exceptional, even in the field of gastroenterology.[18] We believe that the flexible application of such procedures should be mandatory in nephrotic subjects with these characteristics.

An alternative concern raised from the current case is the role of a renal histological analysis in cancer patients with various renal manifestations, including nephrotic syndrome. In patients with carcinomas that are incurable at the moment of diagnosis, a renal biopsy may not be indicated.[11] Although the relationship between malignancies and nephrotic glomerulopathies is somewhat difficult to prove, it may be suggested by clinical characteristics, such as a close temporal link and parallel evolution, including improvement, resolution, and relapse.[11–13,15] Moreover, we should bear in mind that the time to remission of nephrotic syndrome after successful treatment of a malignancy can often be months to years.[11,12,19] Nevertheless, the persistence of nephrotic syndrome with a progression

of chronic renal failure in the current patient obliged us to perform a histological survey in view of the possibility of finding a potentially reversible glomerular lesion.[7] One may argue that pathological assessment of the kidney is not warranted in the milieu of chronic renal insufficiency[20]; however, there was a clinical benefit to performing a renal biopsy in the present patient, because it led us to conclude that the presence of a latent relationship between nephrotic syndrome and gastric malignancy was unlikely, and that our patient was incidentally complicated with gastric carcinoma. In the current case, we faced, as do most physicians at various times, diagnostic dilemmas, not only as to whether to perform a renal biopsy but also with respect to how long it is possible to wait to perform a renal biopsy despite progressive deterioration of the patient's renal function. Obviously, further experience with similar cases is required to resolve such conundrums. The establishment of an optimal management strategy for diabetic patients with both malignancies and various renal manifestations is therefore a matter requiring continuous and careful attention.

Author Contributions

TA drafted the manuscript. NO, ET, and OS made contributions to the acquisition of the clinical data. EK and DN provided a detailed review of the contents and structure of the manuscript, resulting in significant changes to the original document. All authors have read and approved the final manuscript.

REFERENCES

1. Jennette JC, Olson JL, Schwartz MM, Silva FG. Primer on the pathologic diagnosis of renal disease. In: Jennete JC, Olson JL, Schwartz MM, Silvia FG, eds. *Heptinstall's Pathology of the Kidney*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:97–123.
2. Fuiano G, Mazza G, Comi N, et al. Current indications for renal biopsy: a questionnaire-based survey. *Am J Kidney Dis*. 2000;35(3):448–57.
3. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc*. 2003;58(6 suppl):S3–43.
4. Akimoto T, Otake T, Tanaka A, et al. Steroid treatment in patients with membranous nephropathy and hepatitis B virus surface antigenemia: a report of two cases. *Clin Exp Nephrol*. 2011;15(2):289–93.
5. Akimoto T, Ito C, Saito O, et al. Microscopic hematuria and diabetic glomerulosclerosis—clinicopathological analysis of type 2 diabetic patients associated with overt proteinuria. *Nephron Clin Pract*. 2008;109(3):c119–26.
6. Otani N, Akimoto T, Yumura W, et al. Is there a link between diabetic glomerular injury and crescent formation? A case report and literature review. *Diagn Pathol*. 2012;7:46.
7. Sugase T, Akimoto T, Iwazu Y, et al. Minimal change nephrotic syndrome complicated with malignant ascites in a patient with type 2 diabetes. *Intern Med*. 2012;51(14):1885–8.
8. Tone A, Shikata K, Matsuda M, et al. Clinical features of non-diabetic renal diseases in patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2005;69(3):237–42.
9. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. *Clin J Am Soc Nephrol*. 2013;8(10):1718–24.
10. Caramori ML, Parks A, Mauer M. Renal lesions predict progression of diabetic nephropathy in type 1 diabetes. *J Am Soc Nephrol*. 2013;24(7):1175–81.
11. Jefferson JA, Couser WG. Therapy of membranous nephropathy associated with malignancy and secondary causes. *Semin Nephrol*. 2003;23(4):400–5.
12. Ronco PM. Paraneoplastic glomerulopathies: new insights into an old entity. *Kidney Int*. 1999;56(1):355–77.
13. Bacchetta J, Juillard L, Cochat P, Droz JP. Paraneoplastic glomerular diseases and malignancies. *Crit Rev Oncol Hematol*. 2009;70(1):39–58.
14. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976–9 and 1995–7. *Am J Kidney Dis*. 1997;30(5):621–31.
15. Ito C, Akimoto T, Nakazawa E, et al. A case of cervical cancer-related membranous nephropathy treated with radiation therapy. *Intern Med*. 2011;50(1):47–51.
16. Parra-Blanco A, Gimeno-García AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. *J Gastroenterol*. 2010;45(7):703–12.
17. Allard J, Cosby R, Del Giudice ME, Irvine EJ, Morgan D, Tinmouth J. Gastroscopy following a positive fecal occult blood test and negative colonoscopy: systematic review and guideline. *Can J Gastroenterol*. 2010;24(2):113–20.
18. Kim JJ, Han A, Yan AW, Cao D, Laine L. Gastroenterologists' practice patterns for positive fecal occult blood test. *J Clin Gastroenterol*. 2014;48(2):119–26.
19. Pai P, Bone JM, McDicken I, Bell GM. Solid tumor and glomerulopathy. *QJ Med*. 1996;89(5):361–7.
20. Madaio MP. Renal biopsy. *Kidney Int*. 1990;38(3):529–43.

Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 2015; 19(1):30–39
doi: 10.1111/1744-9987.12190

Impact of Metabolic Disturbances and Malnutrition-Inflammation on 6-Year Mortality in Japanese Patients Undergoing Hemodialysis

Naoki Nakagawa,[1] Motoki Matsuki,[1,2] Naoyuki Yao,[2,3] Tomoya Hirayama,[2] Hironori Ishida,[2] Kenjiro Kikuchi,[1,4] and Naoyuki Hasebe[1]

[1]Division of Cardiology, Nephrology, Pulmonology and Neurology, Department of Internal Medicine, Asahikawa Medical University, [2]Departments of Nephrology and Urology, Kitasaito Hospital, [3]Department of Internal Medicine, Asahikawa Rehabilitation Hospital, Asahikawa, and [4]Department of Cardiology, Hokkaido Junkanki Hospital, Sapporo, Japan

Abstract: Metabolic syndrome confers an increased risk of cardiovascular disease (CVD) in the general population. The relationship between adiponectins, and clinical outcomes in patients undergoing hemodialysis remains controversial. We investigated whether adiponectins, biomarkers of inflammation, nutrition status and clinical features predict the mortality of patients undergoing hemodialysis for 6 years. We measured baseline plasma total and high-molecular-weight (HMW) adiponectins, tumor necrosis factor (TNF)-α, serum high sensitivity C-reactive protein (hsCRP), and clinical characteristics including visceral fat area (VFA) and the Geriatric Nutritional Risk Index (GNRI) in 133 patients undergoing chronic hemodialysis. Forty-one of the 133 patients died during follow-up. The deceased patients were significantly older, had more prior CVD and diabetes, higher TNF-α and hsCRP levels but lower GNRI. VFA, and total and HMW adiponectin did not significantly differ between the two groups. TNF-α and hsCRP levels and GNRI score were significant for predicting all-cause and cardiovascular mortality in receiver operating curve analyses. When stratified by a GNRI score of 96, Cox proportional hazards analyses identified TNF-α as a significant predictor of all-cause mortality (hazard ratio [HR] 1.23; $P = 0.038$) and hsCRP as a significant predictor of all-cause and cardiovascular mortality (HR, 2.32, $P = 0.003$; HR 2.30, $P = 0.012$, respectively) after adjusting for age, sex, diabetes mellitus, and prior CVD, only in malnourished patients. These results demonstrate that malnutrition and the inflammatory markers TNF-α and hsCRP, but not metabolic markers, including VFA and adiponectins have a significant impact on 6-year all-cause and cardiovascular mortality in Japanese patients undergoing hemodialysis. **Key Words:** End stage renal disease, Inflammatory cytokine, Malnutrition, Metabolic syndrome.

Metabolic disturbances such as insulin resistance, inflammation and lipid abnormalities are associated with atherosclerosis and cardiovascular death not only in the general population (1–3) but also in patients with chronic kidney disease (4–6). Adipose tissue is not only considered an energy reservoir but also an active endocrine organ that produces several adipocytokines (7). Adiponectin is a multifunctional and abundant adipocytokine with favorable effects on glucose and lipid metabolism, insulin resistance and inflammation (8), and it plays a protective role in experimental models of vascular injury (9). Serum or plasma adiponectin is clinically decreased in pathological states including obesity, diabetes mellitus, and ischemic heart disease (8). Recent studies have found low-, middle- and high-molecular-weight (HMW) adiponectin isoforms in human blood (10). Among these, the HMW isoform is the most active; it is inversely associated with visceral obesity and confers a protective effect on blood vessels. In contrast, the relationship between adiponectin and clinical outcomes in patients undergoing hemodialysis (HD) remain controversial (11,12).

Received December 2013; revised February 2014.
Address correspondence and reprint requests to Dr Naoki Nakagawa, MD, PhD, Division of Cardiology, Nephrology, Pulmonology and Neurology, Department of Internal Medicine, Asahikawa Medical University, 2-1-1-1 Midorigaoka-higashi, Asahikawa, Hokkaido, Japan. Email: naka-nao@asahikawa-med.ac.jp

"Reverse epidemiology" is described as paradoxically better survival of obese patients on HD compared with the general population (13). Several reasons have been proposed to explain the survival bias and temporal discrepancies among competitive risk factors including hypertension, diabetes mellitus and chronic malnutrition-inflammation. Malnutrition and nutritional management are important issues for patients undergoing HD, and regular nutritional assessment is recommended for such patients (14). The Geriatric Nutritional Risk Index (GNRI) is a simple, established nutritional assessment tool with which to assess nutritional status in both elderly individuals (15) and patients undergoing HD (16–18). It is based on only three objective parameters of body weight, height, and serum albumin.

Therefore, we investigated the associations between total and HMW adiponectins, visceral obesity, biomarkers of inflammation, GNRI, and all-cause as well as cardiovascular mortality in Japanese patients undergoing HD during a long-term follow-up.

PATIENTS AND METHODS

Participants

We enrolled 218 patients (age, ≥20 years) who were on maintenance HD for ≥90 days with standard bicarbonate dialysate during March 2006. The HD dose was confirmed using the formula: $Kt/V = -\ln(R - 0.03) + [(4 - 3.5R) \times (UF/W)]$, where Kt/V is the single-pool Kt/V, R is the ratio of post- to pre-dialysis serum urea nitrogen, t is duration of dialysis in hours, UF is ultrafiltration volume in liters, and W is post-dialysis body weight in kilograms (19). Age, gender, lipid parameters, and conventional cardiovascular risk factors were also recorded. After excluding patients with a weekly dialysis duration of <12 h, urea Kt/V of <1.2, use of a temporary HD catheter, and comorbidities with malignancy or infectious diseases, 133 patients (male, $n = 77$; female, $n = 56$; age, 59.8 ± 10.2 y) on maintenance HD for 191.5 ± 112.7 months were enrolled. This study was performed in strict accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethical Scientific Committee of Asahikawa Medical University and Kitasaito Hospital. All study participants provided written informed consent.

Data collection

Blood samples were collected from supine patients into plastic vacuum tubes immediately before the first dialysis session of the week and were separated by centrifugation at $900 \times g$ for 15 min at 4°C. The supernatant was decanted and frozen at −80°C. We used enzyme linked immunosorbent assay kits to measure plasma levels of total and HMW adiponectin (Sekisui Medical, Tokyo, Japan) and tumor necrosis factor (TNF-α) (R&D Systems, Minneapolis, MN, USA) as described previously (20). Other parameters were measured using standard laboratory methods.

Waist circumference (WC; cm) at the umbilical level was measured in patients while standing at the start of dialysis. Body weight refers to dry weight (kg) and body mass index (BMI) was calculated by dividing this by height squared (m^2). We calculated GNRI using serum albumin values, dry weight and ideal body weight. The GNRI was calculated as reported by Yamada et al. (16): $GNRI = [14.89 \times \text{albumin (g/dL)}] + [41.7 \times (\text{weight/ ideal body weight})]$. Note that body weight/ideal body weight was greater than 1 when a subject's body weight exceeded their ideal body weight. Ideal body weight was calculated using height and a BMI of 22, which is reportedly associated with the lowest morbidity rate in the Asian population (21). Smoking was defined as current smoking or a history of habitual smoking. Hypertension was defined as either systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg, or current use of an anti-hypertensive agents. Diabetes was defined as one of the following: fasting blood sugar ≥126 mg/dL, non-fasting blood sugar ≥200 mg/dL, glycosylated hemoglobin (HbA1c) ≥6.0% or current medication with insulin or an oral hypoglycemic agent. Dyslipidemia was defined as total cholesterol ≥220 mg/dL, high-density lipoprotein (HDL) cholesterol <40 mg/dL for men, <50 mg/dL for women, triglycerides ≥150 mg/dL or medication with anti-hyperlipidemic agents. The criteria for metabolic syndrome were based on a modified version of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure (Adult Treatment Panel III) (22), and defined metabolic syndrome as the presence of 3 or more of the following 5 components: (i) medication for hypertension or systolic blood pressure ≥130 and/or diastolic pressure ≥85 mmHg; (ii) triglycerides ≥150 mg/dL, (iii) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women; (iv) medication for diabetes or HbA1c ≥6.0%; and (v) WC ≥85 cm for men and ≥90 cm for women (21). We assessed HbA1c because fasting glucose data were available only from a subsample of fasting patients.

Abdominal fat distribution was determined using abdominal computed tomography (CT) at the level of the umbilicus as described previously (20). Subcutaneous fat tissue was defined as extraperitoneal fat

between the skin and muscle. Intra-abdominal tissue with the same density as subcutaneous fat tissue was defined as visceral fat. Subcutaneous (SFA) and visceral fat areas (VFA) were also measured at the level of the umbilicus. Aortic calcification scores (AOCS) were estimated using abdominal CT with 3-mm collimation, 5-mm slice thickness and a 35-cm field of view. Brightness scores on images were adjusted using a standard phantom and calcium levels were determined in a 10-cm segment of the distal abdominal aorta above the aortic bifurcation. Calcification, defined as areas of >1 mm^2 with a density of >130 Hounsfield units, was quantified using the Agatston scores generated by Aqualion offline software (Toshiba, Tokyo, Japan) as described previously (23).

Follow-up

Follow-up data were retrieved from clinical records and/or death certificates by personnel blinded to the anthropometric, body composition and laboratory assessments. The follow-up began on the date of enrollment and finished at death from any causes or 20 March 2012, whichever came first. No patient was lost to follow-up.

Statistical analysis

Results are expressed as means ± standard deviations. Baseline characteristics between deceased and surviving groups were compared using the *t*-test, χ^2 test, and the Mann–Whitney *U*-test as appropriate. Continuous variables were assessed using univariate and multivariate linear regression. Receiver-operating characteristics (ROC) curves for GNRI, TNF-α, hsCRP, total and HMW adiponectin, BMI, WC, and VFA levels at baseline were constructed and areas under the ROC curves (AUC) were calculated. The optimal cut-off value was considered the maximum difference of sensitivity and 1- specificity (Youden index). Figure 1 shows the optimal cutoff for malnutrition (GNRI ≤ 96) as well as the sensitivity, specificity, and accuracy for predicting all-cause mortality at the end of the follow-up period. Confidence intervals (CI) for areas under the ROC curves were calculated using nonparametric assumptions. Survival was determined from Kaplan–Meier curves. Independent variables were defined, and survival was compared between groups stratified by the presence or absence of malnutrition using Cox proportional hazards models. Adjusted hazard ratios (HR) with 95% CIs are reported. *P*-values <0.05 were considered significant. All data were analyzed using SPSS ver. 19.0 for Windows (SPSS, Chicago, IL, USA).

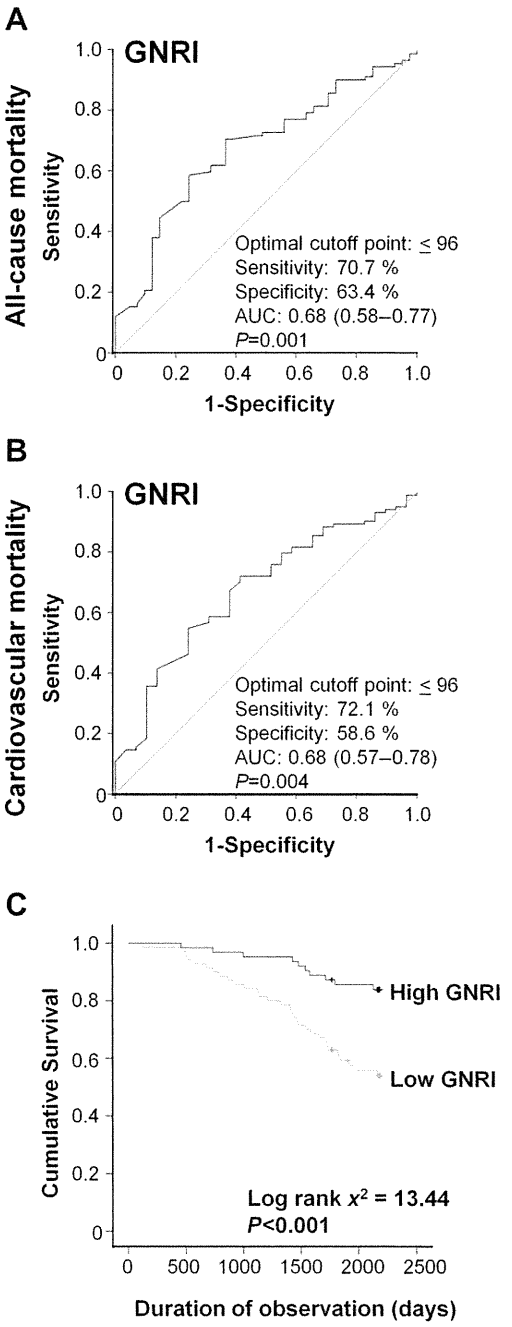


FIG. 1. Mortality among patients undergoing hemodialysis as predicted by malnutrition.
Receiver operating characteristic (ROC) curves for predicting all-cause (A) and cardiovascular (B) mortality constructed using the baseline score on the Geriatric Nutritional Risk Index (GNRI). The optimal GNRI cutoff was determined along with sensitivity, specificity and accuracy for predicting mortality at the end of the follow-up. (C) Kaplan–Meier curves for all-cause mortality relative to baseline GNRI (≤ 96 or >96) stratified by cutoff.

RESULTS

Clinical characteristics

The mean age of the 133 patients at baseline was 59.8 ± 10.2 years, 57.9% were male, 26.3% had diabetes, and 38.3 % had metabolic syndrome. During the 6-year follow up period, 41 (30.9%) patients died (heart failure, $n = 13$; acute myocardial infarction, $n = 11$; stroke, $n = 2$; infection, $n = 10$; and malignant cancer, $n = 5$). Table 1 shows the baseline characteristics of the deceased and surviving patients. The duration of HD, sex, and adequacy of dialysis as indicated by Kt/V urea did not significantly differ between the two groups. Deceased patients were significantly older, had a higher frequency of prior CVD and diabetes, higher levels of TNF-α, hsCRP, and AOCS but lower levels of serum albumin and creatinine, suggesting that deceased patients had more malnourished and inflammatory status than survived patients. Hemoglobin, total cholesterol, triglycerides, total and HMW adiponectin, the number of components of metabolic syndrome, and the prevalence of metabolic syndrome did not significantly differ between the groups. Table 2 shows the body composition, fat distribution and adipocytokines according to sex in

TABLE 1. *Baseline characteristics of the patients*

	Total	Death	Survival	*P*-value
Number	133	41	92	–
Age, years	59.8 ± 10.2	64.5 ± 8.3	57.7 ± 10.2	<0.001
Gender, male	77 (58%)	26 (63%)	51 (55%)	0.391
Duration of dialysis, months	191.5 ± 112.7	189.5 ± 115.6	192.4 ± 112.0	0.755
Kt/V urea	1.3 ± 0.3	1.4 ± 0.3	1.3 ± 0.2	0.220
Hypertension	101 (76%)	30 (73%)	71 (77%)	0.667
Diabetes	35 (26%)	18 (44%)	17 (18%)	0.002
Dyslipidemia	17 (13%)	2 (5%)	15 (16%)	0.067
Metabolic syndrome	51 (38%)	20 (49%)	31 (34%)	0.100
Smoking	52 (39%)	17 (42%)	35 (38%)	0.567
Prior cardiovascular disease	37 (28%)	6 (15%)	50 (54%)	<0.001
Body weight/Dry weight, kg	54.2 ± 9.5	53.5 ± 9.3	54.5 ± 9.6	0.536
Body mass index, kg/m^2	21.4 ± 2.8	21.2 ± 2.8	21.4 ± 2.8	0.777
Waist circumference, cm	82.2 ± 9.0	81.7 ± 9.3	81.5 ± 8.8	0.233
Subcutaneous fat area, cm^2	87.8 ± 46.9	92.6 ± 51.4	85.8 ± 45.0	0.522
Visceral fat area, cm^2	68.2 ± 44.0	74.2 ± 48.2	65.7 ± 42.1	0.406
Systolic blood pressure, mm Hg	147.0 ± 20.1	141.5 ± 20.7	149.6 ± 19.3	0.055
Diastolic blood pressure, mm Hg	83.2 ± 14.7	77.3 ± 16.1	86.1 ± 13.2	0.011
Pulse pressure, mm Hg	63.7 ± 16.7	64.2 ± 17.8	63.5 ± 16.3	0.770
Hemoglobin, g/dL	10.7 ± 1.2	10.7 ± 1.3	10.7 ± 1.2	0.713
Hematocrit, %	31.4 ± 3.5	31.7 ± 3.8	31.3 ± 3.4	0.774
Serum total cholesterol, mg/dL	147.3 ± 32.4	145.5 ± 26.7	148.1 ± 34.7	0.844
Serum triglycerides, mg/dL	108.4 ± 61.0	99.5 ± 41.1	112.3 ± 67.7	0.649
Serum HDL-cholesterol, mg/dL	45.1 ± 11.0	43.8 ± 8.6	45.7 ± 11.9	0.721
Serum LDL-cholesterol, mg/dL	80.6 ± 26.4	82.4 ± 22.1	79.8 ± 28.1	0.498
Serum uric acid, mg/dL	7.1 ± 1.2	7.0 ± 1.1	7.1 ± 1.3	0.938
Serum potassium, mEq/L	4.9 ± 0.7	4.8 ± 0.7	4.9 ± 0.6	0.285
Serum calcium, mg/dL	9.2 ± 0.8	9.0 ± 0.9	9.2 ± 0.8	0.119
Serum phosphate, mg/dL	5.8 ± 1.6	5.8 ± 1.5	5.8 ± 1.6	0.936
Serum intact PTH, pg/mL	138.2 ± 146.4	146.9 ± 175.3	134.6 ± 133.3	0.790
Serum albumin, g/dL	3.9 ± 0.3	3.7 ± 0.2	3.9 ± 0.3	<0.001
Serum urea, mg/dL	62.0 ± 15.3	58.2 ± 16.0	63.7 ± 14.8	0.033
Serum creatinine, mg/dL	11.2 ± 2.9	9.9 ± 2.2	11.8 ± 3.0	<0.001
Hemoglobin A1c, %	5.3 ± 1.1	5.5 ± 0.9	5.1 ± 1.1	0.295
Number of components of metabolic syndrome	2.2 ± 1.2	2.4 ± 1.1	2.1 ± 1.2	0.094
Plasma total adiponectin, μg/mL	10.7 ± 4.9	11.7 ± 5.1	10.2 ± 4.8	0.143
Plasma HMW adiponectin, μg/mL	5.0 ± 3.2	5.8 ± 3.8	4.7 ± 2.8	0.196
Plasma TNF-α, pg/mL	4.3 ± 1.7	5.0 ± 1.8	4.0 ± 1.6	0.001
Serum hsCRP, mg/dL	0.27 ± 0.45	0.47 ± 0.65	0.18 ± 0.29	0.006
Geriatric nutritional risk index	96.4 ± 5.1	94.5 ± 4.4	97.3 ± 5.2	0.001
Aortic calcification score	33.7 ± 24.2	42.9 ± 23.0	29.9 ± 23.8	0.004

Variables are presented as mean ± standard deviation, or number (percentage). HDL, high-density lipoprotein; Kt/V denotes fractional urea clearance; LDL, low-density lipoprotein; PTH, parathyroid hormone.

TABLE 2. *Body composition, fat accumulation, adiponectins, and inflammation markers according to sex*

	Death		Survival	
	Men	Women	Men	Women
Number	26	15	51	41
Body weight/Dry weight, kg	56.3 ± 8.3*†	48.5 ± 9.1	60.9 ± 5.9*	46.5 ± 7.0
Body mass index, kg/m^2	21.3 ± 2.4	21.1 ± 3.4	22.2 ± 2.2*	20.4 ± 3.2
Waist circumference, cm	83.6 ± 8.7	83.9 ± 10.7	84.4 ± 6.8*	78.1 ± 9.7
Subcutaneous fat area, cm^2	77.4 ± 46.9	116.8 ± 50.2	85.2 ± 44.2	86.5 ± 46.4
Visceral fat area, cm^2	77.5 ± 51.9	68.9 ± 42.8	76.5 ± 42.0	52.7 ± 38.8
Plasma total adiponectin, μg/mL	11.1 ± 4.8	12.8 ± 5.8	9.2 ± 4.3	11.6 ± 5.0
Plasma HMW adiponectin, μg/mL	5.1 ± 3.1	6.8 ± 4.7	4.0 ± 2.6	5.5 ± 2.9
Plasma TNF-α, pg/mL	5.2 ± 2.0 †	4.7 ± 1.6	3.8 ± 1.3	4.4 ± 1.8
Serum hsCRP, mg/dL	0.41 ± 0.54	0.57 ± 0.81†	0.21 ± 0.31	0.14 ± 0.26

Variables are presented as mean ± standard deviation or percentage. *$P < 0.05$ vs. men in the same group and †$P < 0.05$ vs. same gender of survivors. HMW, high molecular weight; hsCRP, high-sensitivity C-reactive protein; TNF, tumor necrosis factor.

the two groups. Although mean BMI and WC were greater in the men who survived, VFA, SFA, and total and HMW adiponectin did not differ significantly between males and females in either groups.

Follow-up data

All AUCs of the ROC for the malnutrition marker GNRI (Fig. 1), and the inflammation markers TNF-α and hsCRP (Fig. 2) for predicting all-cause and cardiovascular mortality were >0.65 (Figs 1A,B,2). All *P*-values for the AUCs of these parameters were significant at $P < 0.05$. In contrast, all AUCs of the ROC for the metabolic markers, BMI, WC, VFA, and total and HMW adiponectin levels for predicting all-cause and cardiovascular mortality were <0.60 and not significant (Fig. 3), suggesting that metabolic parameters do not impact mortality in patients undergoing HD.

Next, we analyzed independent determinants for all-cause and cardiovascular mortality using multiple linear regression analyses. Age, diabetes, prior CVD,

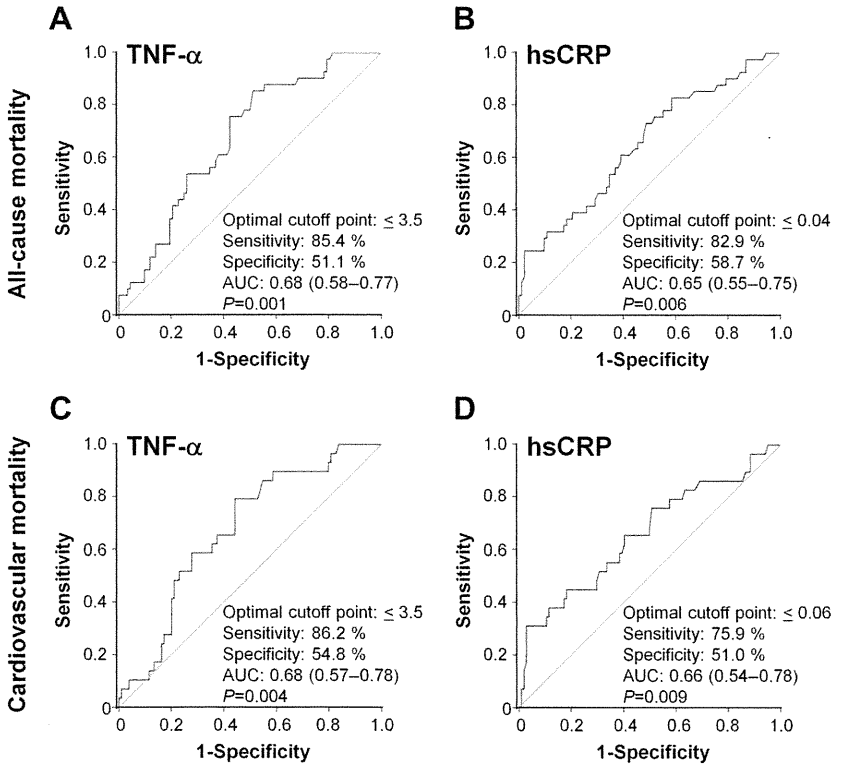


FIG. 2. Inflammation markers for predicting mortality of patients undergoing hemodialysis.
All-cause (A and B) and cardiovascular (C and D) mortality predicted from receiver operating characteristics (ROC) curves constructed using baseline values for tumor necrosis factor-alpha (TNF-α) (A and C) and high sensitivity C-reactive protein (hsCRP) (B and D).

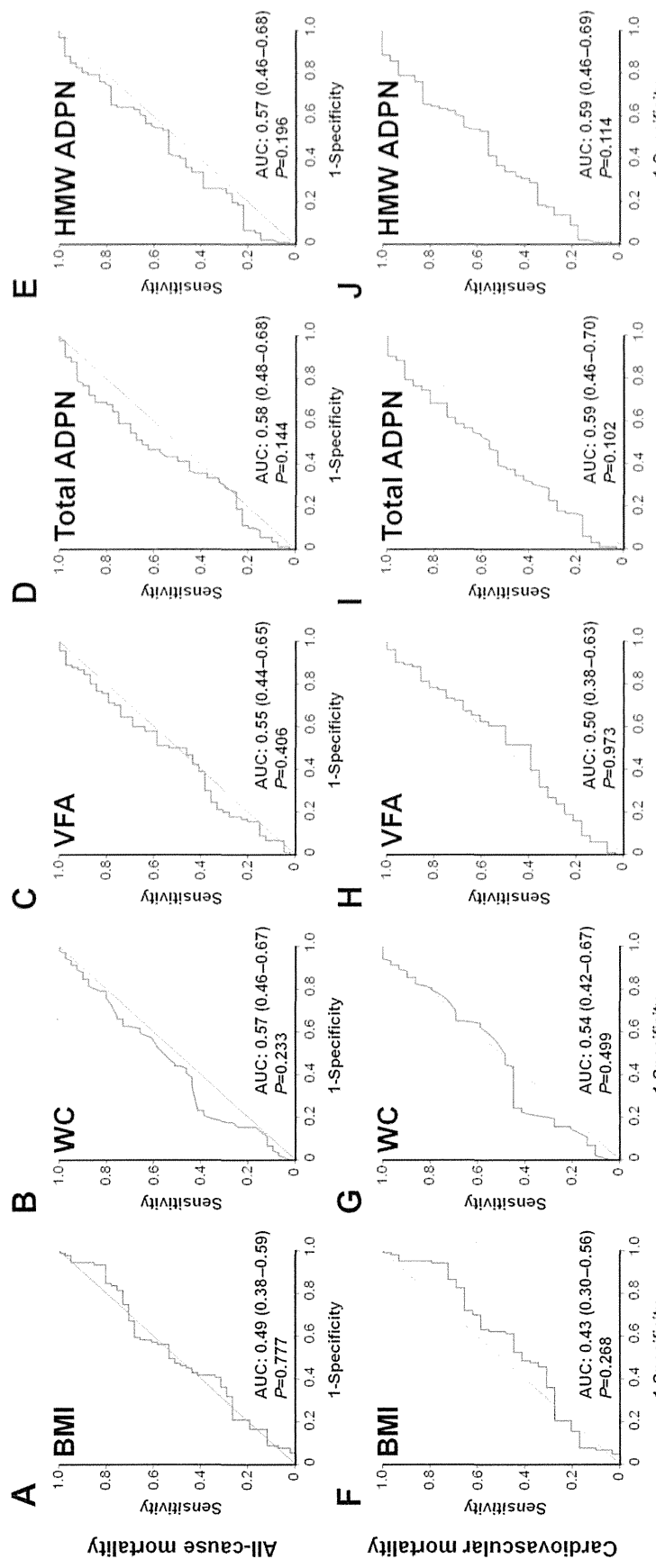


FIG. 3. Body mass index (BMI), waist circumference (WC), visceral fat area (VFA), and total and high-molecular-weight (HMW) adiponectins as metabolic markers for predicting mortality of patients undergoing hemodialysis.
ROC curves for predicting all-cause (A–E) and cardiovascular (F–J) mortality constructed using baseline values for BMI (A, F), WC (B, G), VFA (C, H), total adiponectin (D, I), and HMW adiponectin (E, J).

TABLE 3. *Multiple linear regression analysis to assess predictors of all-cause and cardiovascular mortality in patients undergoing hemodialysis*

	All-cause mortality			Cardiovascular mortality		
Model 1	B	β	*P*	B	β	*P*
TNF-α	0.045	0.158	0.042	0.024	0.098	0.230
Age	0.008	0.177	0.028	0.005	0.126	0.121
Sex (M = 1)	0.080	0.086	0.281	-0.033	-0.039	0.626
Diabetes	0.216	0.206	0.009	0.190	0.202	0.011
Prior cardiovascular disease	0.246	0.223	0.008	0.298	0.301	0.001
GNRI	−0.016	−0.180	0.030	−0.010	−0.125	0.133
	All-cause mortality			Cardiovascular mortality		
Model 2	B	β	*P*	B	β	*P*
hsCRP	0.204	0.198	0.011	0.196	0.213	0.007
Age	0.008	0.185	0.019	0.005	0.124	0.144
Sex (M = 1)	0.067	0.072	0.357	−0.042	−0.050	0.520
Diabetes	0.172	0.164	0.035	0.151	0.161	0.040
Prior cardiovascular disease	0.269	0.243	0.003	0.311	0.315	0.001
GNRI	−0.016	−0.180	0.027	−0.010	−0.118	0.146

GNRI, Geriatric Nutritional Risk Index; hsCRP, high-sensitivity C-reactive protein; TNF, tumor necrosis factor. Model 1, *F* ratio = 8.323; $r^2 = 0.284$ ($P < 0.001$) for all-cause, *F* ratio = 7.468; $r^2 = 0.262$ ($P < 0.001$) for cardiovascular mortality. Model 2, *F* ratio = 9.152; $r^2 = 0.304$ ($P < 0.001$) for all-cause, *F* ratio = 8.854; $r^2 = 0.297$ ($P < 0.001$) for cardiovascular mortality. B, unstandardized coefficients; β, standardized coefficients.

TNF-α and hsCRP were positively associated, whereas GNRI level was negatively associated with all-cause mortality (Table 3). In contrast, diabetes, prior CVD, and hsCRP levels were positively associated with cardiovascular mortality, suggesting that hsCRP is a more useful predictive marker of cardiovascular mortality than TNF-α.

We further examined the impact of TNF-α and hsCRP on mortality stratified by the presence or absence of malnutrition defined as GNRI ≤ 96 based on the ROC curve results (Fig. 1A,B). Based on ROC analyses for predicting all-cause mortality at the end of the follow-up period, the optimal cutoff points for TNF-α and hsCRP were 3.5 pg/mL (Fig. 2A) and 0.04 mg/dL (Fig. 2B), respectively. Figure 4 shows the Kaplan–Meier curves for all-cause and cardiovascular mortality. Higher TNF-α and hsCRP levels were both associated with higher all-cause ($P = 0.002$ and 0.030, respectively; Fig. 4A,B) and cardiovascular mortality ($P = 0.003$ and 0.042, respectively; Fig. 4E,F) in malnourished patients. In contrast, higher hsCRP was only associated with higher cardiovascular mortality in patients who were not malnourished ($P = 0.048$; Fig. 4H), whereas higher TNF-α and hsCRP levels were not associated with all-cause mortality (Fig. 4C,D).

Finally, we investigated the role of inflammation markers as a potential modifier of the relationships between independent variables and either all-cause or cardiovascular mortality using Cox proportional hazards models. Both TNF-α and hsCRP were positively associated with all-cause and cardiovascular mortality in malnourished patients (GNRI ≤ 96) after adjusting for age, sex, prior CVD, and diabetes mellitus (Table 4). In contrast, hsCRP was positively associated with cardiovascular mortality, whereas inflammation markers and all-cause mortality were not significantly associated (GNRI > 96) in patients who were not malnourished (Table 4). These inflammation markers served as useful predictors of all-cause and cardiovascular mortality, particularly in malnourished patients.

DISCUSSION

Our results clearly demonstrate that the predictive value of TNF-α and hsCRP levels on 6-year all-cause and cardiovascular mortality was critically dependent on nutrition status in Japanese patients undergoing HD. In contrast, metabolic parameters such as total and HMW adiponectins, BMI, WC and VFA, were not associated with all-cause and cardiovascular mortality in those patients. These findings emphasize the importance of malnutrition as a cause of reverse epidemiology.

Geriatric Nutritional Risk Index was originally used to predict malnutrition-related complications and mortality in hospitalized elderly patients, and

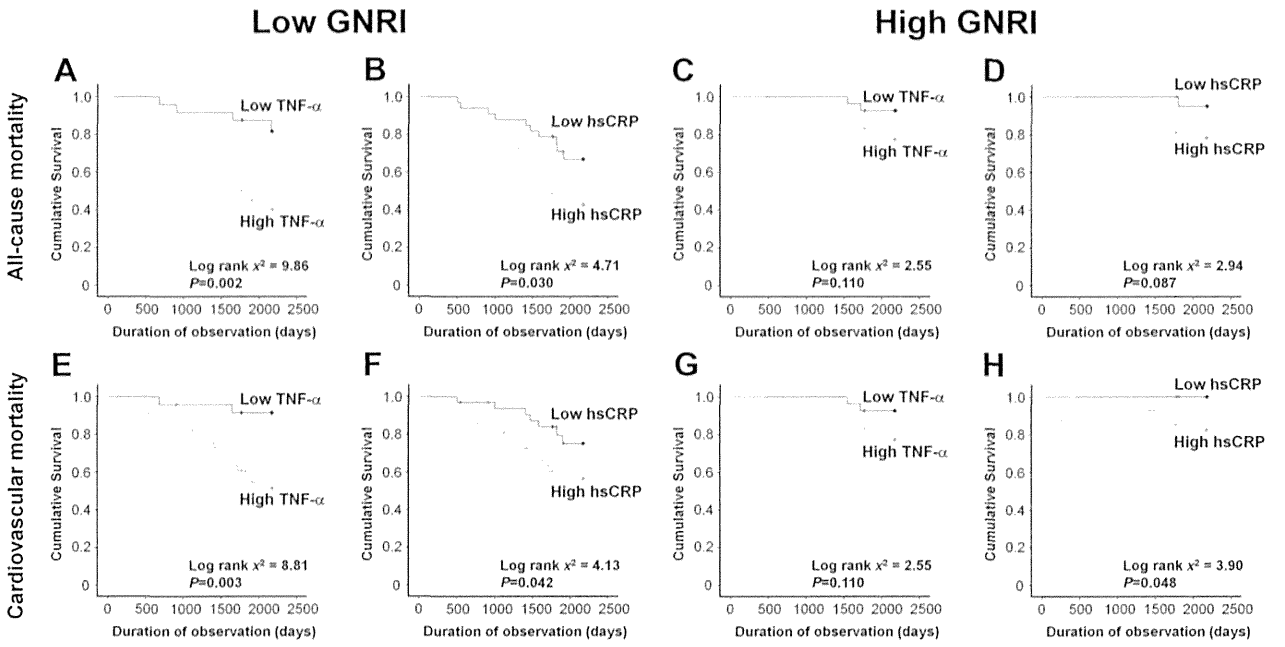


FIG. 4. Kaplan–Meier mortality curves for patients undergoing hemodialysis according to tumor necrosis factor-α (TNF-α) and high sensitivity C-reactive protein (hsCRP) and modified by nutritional status.
All-cause (A–D) and cardiovascular (E–H) mortality relative to baseline TNF-α (A, C, E, G) and hsCRP (B, D, F, H) levels modified by GNRI ≤ 96 (A, B, E, F) and >96 (C, D, G, H).

the defined cut-off values according to weight loss and albumin concentrations were: GNRI < 82, major nutrition-related risk; 82 to <92, moderate nutrition-related risk; 92 to ≤ 98, low nutrition-related risk; >98, no risk (15). The GNRI value in patients undergoing HD has recently been studied. Yamada et al. reported that the most accurate GNRI cutoff value based on malnutrition–inflammation scores to identify malnourished patients is <91.2 (16), whereas other studies set the GNRI cut-off for mortality at 90 based on the highest positive likelihood and risk ratios (17,18). The present ROC curve analysis

TABLE 4. *Hazard ratios for all-cause and cardiovascular mortality according to Cox regression proportional hazards analysis stratified by Geriatric Nutritional Risk Index (GNRI) value*

	GNRI ≤ 96				GNRI > 96			
	All-cause mortality		Cardiovascular mortality		All-cause mortality		Cardiovascular mortality	
Model 1	HR (CI, 95%)	*P*	HR (CI, 95%)	*P*	HR (CI, 95%)	*P*	HR (CI, 95%)	*P*
TNF-α	1.23 (1.01–1.51)	0.038	1.19 (0.94–1.52)	0.157	1.28 (0.78–2.08)	0.332	1.25 (0.74–2.12)	0.399
Age	1.02 (0.98–1.07)	0.330	1.03 (0.98–1.09)	0.248	1.10 (1.01–1.20)	0.030	1.08 (0.98–1.20)	0.136
Sex (M = 1)	1.70 (0.81–3.56)	0.330	1.07 (0.44–2.56)	0.889	4.12 (0.47–36.4)	0.203	2.54 (0.27–24.3)	0.418
Diabetes	1.75 (0.82–3.73)	0.151	2.21 (0.92–5.32)	0.077	2.39 (0.63–9.08)	0.202	1.95 (0.38–10.1)	0.427
Prior CVD	3.13 (1.43–6.84)	0.004	4.39 (1.72–11.2)	0.002	0.98 (0.18–5.41)	0.979	1.55 (0.25–9.77)	0.638
	GNRI ≤ 96				GNRI > 96			
	All-cause mortality		Cardiovascular mortality		All-cause mortality		Cardiovascular mortality	
Model 2	HR (CI, 95%)	*P*	HR (CI, 95%)	*P*	HR (CI, 95%)	*P*	HR (CI, 95%)	*P*
hsCRP	2.32 (1.34–4.04)	0.003	2.30 (1.20–4.40)	0.012	2.38 (0.56–10.1)	0.242	5.37 (1.14–25.2)	0.033
Age	1.03 (0.98–1.07)	0.238	1.03 (0.98–1.09)	0.213	1.11 (1.02–1.20)	0.018	1.09 (0.98–1.21)	0.099
Sex (M = 1)	1.46 (0.70–3.04)	0.310	0.92 (0.38–2.19)	0.843	4.55 (0.52–40.0)	0.172	3.77 (0.40–35.5)	0.247
Diabetes	1.52 (0.71–3.27)	0.281	1.89 (0.78–4.60)	0.158	1.74 (0.47–6.46)	0.411	0.99 (0.19–5.17)	0.986
Prior CVD	3.62 (1.67–7.88)	0.001	5.28 (2.06–13.6)	0.001	1.49 (0.30–7.44)	0.628	3.05 (0.51–18.4)	0.224

CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; TNF, tumor necrosis factor.

for all-cause 6-year mortality found significantly increased all-cause and cardiovascular mortality in patients with GNRI ≤ 96 compared with that >96, suggesting that the predictive value of GNRI for mortality among patients undergoing HD might be 96, although this cutoff was higher than those in other studies (16–18) and included patients at moderate nutrition-related risk. Further prospective investigations are required to confirm the optimal value in patients undergoing dialysis.

Inflammatory markers, including TNF-α and hsCRP, are powerful independent risk factors for atherosclerosis, CVD, and mortality in patients with end stage renal disease (24,25). We also found that TNF-α and hsCRP were positively associated with all-cause and cardiovascular mortality after adjusting for age, sex, prior CVD, and diabetes mellitus. When stratifying by a GNRI of 96, TNF-α and hsCRP were positively associated with all-cause and cardiovascular mortality only in patients with a GNRI ≤ 96. Furthermore, hsCRP was positively associated with cardiovascular mortality even in patients who were not malnourished, whereas TNF-α was not, suggesting that different pathways trigger these markers. These findings show that the impact of inflammatory markers differs according to nutrition status and that these inflammation markers are useful to predict all-cause and cardiovascular mortality, particularly in patients undergoing HD with severe to moderate malnutrition.

In the present study, the prevalence of metabolic syndrome in patients undergoing HD was 38.3%, consistent with the findings of recent studies which are reported from 40% to 60% (26–31). Metabolic syndrome is considered as a predictive parameter of mortality for patients undergoing HD (11,12), and predicts hospitalization in these patients (28). In contrast, we found that metabolic parameters such as BMI, WC, VFA, and total and HMW adiponectin levels were not associated with all-cause or cardiovascular mortality in patients undergoing HD as in recent studies (32,33). Possible explanations for the discrepancies among these studies are differences in the study populations, inclusion criteria, dialysis method, confounding influences of covariates, and different retention of the various adiponectin isoforms in patients with residual kidney function. Interestingly, a recent study about metabolic syndrome in patients undergoing HD as a risk factor for new-onset diabetes mellitus after renal transplant was reported (34). Therefore, further prospective investigations are required to confirm the role of metabolic disturbances in patients undergoing HD.

CONCLUSIONS

Malnutrition and the inflammatory markers tumor necrosis factor-α and high sensitivity C-reactive protein, but not metabolic markers, including visceral obesity and adiponectins had a significant impact on 6-year all-cause and cardiovascular mortality in Japanese patients undergoing hemodialysis. Appropriate management of malnutrition in such patients is critical to improve survival.

Acknowledgments: This study was supported, in part, by a Grant-in-Aid for Progressive Renal Diseases Research, Research on Rare and Intractable Disease, from the Ministry of Health, Labor and Welfare of Japan. We thank Kozue Kanzaki and the Kitasaito Hospital staff for help with data collection.

Conflict of interest: none declared.

REFERENCES

1. Isomaa B, Almgren P, Tuomi T et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001;24:683–9.
2. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–52.
3. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabet Med* 2006;23:469–80.
4. Peralta CA, Kurella M, Lo JC, Chertow GM. The metabolic syndrome and chronic kidney disease. *Curr Opin Nephrol Hypertens* 2006;15:361–5.
5. Thomas G, Sehgal AR, Kashyap SR, Srinivas TR, Kirwan JP, Navaneethan SD. Metabolic syndrome and kidney disease: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2011;6:2364–73.
6. Singh AK, Kari JA. Metabolic syndrome and chronic kidney disease. *Curr Opin Nephrol Hypertens* 2013;22:198–203.
7. Westerink J, Visseren FL. Pharmacological and non-pharmacological interventions to influence adipose tissue function. *Cardiovasc Diabetol* 2011;10:13.
8. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. *Arterioscler Thromb Vasc Biol* 2004;24:29–33.
9. Peake PW, Kriketos AD, Campbell LV, Shen Y, Charlesworth JA. The metabolism of isoforms of human adiponectin: studies in human subjects and in experimental animals. *Eur J Endocrinol* 2005;153:409–17.
10. Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005;26:439–51.
11. Zoccali C, Mallamaci F, Tripepi G et al. Adiponectin, metabolic risk factors, and cardiovascular events among patients with end-stage renal disease. *J Am Soc Nephrol* 2002;13:134–41.
12. Rao M, Li L, Tighiouart H, Jaber BL, Pereira BJ, Balakrishnan VS. Plasma adiponectin levels and clinical outcomes among haemodialysis patients. *Nephrol Dial Transplant* 2008;23:2619–28.
13. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in

maintenance dialysis patients. *Kidney Int* 2003;63:793–808.
14. Silverberg DS, Wexler D, Blum M, Iaina A. The Cardio Renal Anemia Syndrome: correcting anemia in patients with resistant congestive heart failure can improve both cardiac and renal function and reduce hospitalizations. *Clin Nephrol* 2003;60:S93–S102.
15. Bouillanne O, Morineau G, Dupont C et al. Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr* 2005;82:777–83.
16. Yamada K, Furuya R, Takita T et al. Simplified nutritional screening tools for patients on maintenance hemodialysis. *Am J Clin Nutr* 2008;87:106–13.
17. Kobayashi I, Ishimura E, Kato Y et al. Geriatric Nutritional Risk Index, a simplified nutritional screening index, is a significant predictor of mortality in chronic dialysis patients. *Nephrol Dial Transplant* 2010;25:3361–5.
18. Park JH, Kim SB, Shin HS, Jung YS, Rim H. Geriatric nutritional risk index may be a significant predictor of mortality in Korean hemodialysis patients: a single center study. *Ther Apher Dial* 2012;16:121–6.
19. Daugirdas JT. 2nd-generation logarithmic estimates of single-pool variable volume Kt/V—an analysis of error. *J Am Soc Nephrol* 1993;4:1205–13.
20. Nakagawa N, Yao N, Hirayama T et al. Potential impact of renin-angiotensin system inhibitors and calcium channel blockers on plasma high-molecular-weight adiponectin levels in hemodialysis patients. *Hypertens Res* 2011;34:592–8.
21. Matsuzawa Y, Nakamura T, Takahashi M et al. New criteria for "obesity disease" in Japan. *Circ J* 2002;66:987–92.
22. Grundy SM, Cleeman JI, Merz CNB et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;110:227–39.
23. Talib A, Nakagawa N, Saito E et al. The balance of fetuin-A and osteoprotegerin is independently associated with diastolic dysfunction in hemodialysis patients. *Hypertens Res* 2012;35:426–33.
24. Tripepi G, Mallamaci F, Zoccali C. Inflammation markers, adhesion molecules, and all-cause and cardiovascular mortality in patients with ESRD: searching for the best risk marker by multivariate modeling. *J Am Soc Nephrol* 2005;16(Suppl 1):S83–8.
25. Wang AY, Lam CW, Wang M et al. Increased circulating inflammatory proteins predict a worse prognosis with valvular calcification in end-stage renal disease: a prospective cohort study. *Am J Nephrol* 2008;28:647–53.
26. Tu SF, Chou YC, Sun CA, Hsueh SC, Yang T. The prevalence of metabolic syndrome and factors associated with quality of dialysis among hemodialysis patients in Southern Taiwan. *Glob J Health Sci* 2012;4:53–62.
27. Ucar E, Huzmeli C, Guven O et al. Frequency of metabolic syndrome among hemodialysis patients according to NCEP-ATP III and IDF definitions. *Ren Fail* 2009;31:221–8.
28. Yang SY, Chiang CK, Hsu SP et al. Metabolic syndrome predicts hospitalization in hemodialysis patients: a prospective Asian cohort study. *Blood Purif* 2007;25:252–9.
29. Rasic-Milutinovic Z, Perunicic G, Pljesa S, Gluvic Z, Ilic M, Stokic E. Metabolic syndrome in HD patients: association with body composition, nutritional status, inflammation and serum iron. *Intern Med* 2007;46:945–51.
30. Tsangalis G, Papaconstantinou S, Kosmadakis G, Valis D, Zerefos N. Prevalence of the metabolic syndrome in hemodialysis. *Int J Artif Organs* 2007;30:118–23.
31. Lee CC, Lee RP, Subeq YM, Wang CH, Fang TC, Hsu BG. Fasting serum total ghrelin level inversely correlates with metabolic syndrome in hemodialysis patients. *Arch Med Res* 2008;39:785–90.
32. Tsai YC, Lee CT, Huang TL et al. Inflammatory marker but not adipokine predicts mortality among long-term hemodialysis patients. *Mediators Inflamm* 2007;2007:19891.
33. Kollerits B, Fliser D, Heid IM, Ritz E, Kronenberg F, Grp MS. Gender-specific association of adiponectin as a predictor of progression of chronic kidney disease: the Mild to Moderate Kidney Disease Study. *Kidney Int* 2007;71:1279–86.
34. Bonet J, Martinez-Castelao A, Bayes B. Metabolic syndrome in hemodialysis patients as a risk factor for new-onset diabetes mellitus after renal transplant: a prospective observational study. *Diabetes Metab Syndr Obes* 2013;6:339–46.

Cerebral Microbleeds and Asymptomatic Cerebral Infarctions in Patients with Atrial Fibrillation

Tsukasa Saito, MD, PhD,* Yuichiro Kawamura, MD, PhD,* Yasuko Tanabe, MD, PhD,* Asuka Asanome, MD,* Kae Takahashi, MD,* Jun Sawada, MD, PhD,* Takayuki Katayama, MD, PhD,* Nobuyuki Sato, MD, PhD,* Hitoshi Aizawa, MD, PhD,† and Naoyuki Hasebe, MD, PhD*

Background: Atrial fibrillation (AF) is a cardiac arrhythmia that does not infrequently induce ischemic strokes; however, little research has been reported on focal cerebral microangiopathic lesions in patients with AF. Recently cerebral microbleeds (CMBs) have been noticed for their potential implication in cerebral small vessel disease. Therefore, we had 2 goals in the present study: (1) to compare the prevalence of CMBs in patients with AF with that in patients without AF, and (2) to prove that CMBs could be a clinical predictive factor for the development of future cerebral microangiopathy in patients with AF without a history of symptomatic cerebral infarction in a prospective manner. *Methods:* We performed yearly brain magnetic resonance imaging (MRI) assessments for a maximum of 5 years in 131 patients with AF and 112 control patients. Seventy-seven patients with AF underwent more than 3 yearly MRI scans. *Results:* The Kaplan–Meier curve showed that the development of an asymptomatic cerebral infarction (ACI) was associated with the baseline presence of a CMB ($P = .004$). A multivariate Cox regression analysis revealed that the CMBs at baseline were significantly associated with an increment in not only the occurrence of ACIs (hazard ratio [HR], 5.414; 95% confidence interval [CI], 1.03-28.43; $P = .046$) but also in the consecutive development of CMBs (HR, 6.274; 95% CI, 1.43-27.56; $P = .015$). *Conclusions:* Patients with AF had a significantly higher prevalence of CMBs. The presence of CMBs in the baseline MRI may predict the consequent onset of an ACI and increase in CMBs in patients with AF. **Key Words:** Microbleeds—atrial fibrillation—cerebral small vessels—cerebral infarction.

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia that does not infrequently induce ischemic strokes. It is well known that the incidence of a cardiogenic embolism in patients with nonvalvular AF increases in proportion to the $CHADS_2$ (1 point for congestive heart failure, hypertension, age 75 years, and diabetes, and 2 points for previous stroke/transient ischemic attack [TIA]) score.[1] The $CHADS_2$ score makes us aware that some of its components also play a key role in focal cerebral microangiopathy. Although there are several reports on hemostasis or excessive blood clotting influencing left atrial

From the *Department of Internal Medicine, Cardiovascular, Respiratory and Neurology Division, Asahikawa Medical University, Asahikawa, Hokkaido; and †Department of Neurology, Tokyo Medical University, Tokyo, Japan.

Received November 18, 2013; revision received December 28, 2013; accepted January 7, 2014.

Address correspondence to Tsukasa Saito, MD, PhD, Department of Internal Medicine, Cardiovascular, Respiratory and Neurology Division, Asahikawa Medical University, Midorigaoka Higashi 2-1-1-1, Asahikawa, Hokkaido 078-8510, Japan. E-mail: tsukasa@asahikawa-med.ac.jp.

1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.01.005

thromboses in AF, only a few reports have addressed focal cerebral microangiopathy in patients with AF.

Cerebral microbleeds (CMBs) are seen as small, 2-5 mm in diameter, round foci with hypointensity on the gradient echo (GRE) T2*-weighted magnetic resonance imaging (MRI).[2,3] Several investigators have speculated that CMBs represent a perivascular accumulation of hemosiderin-containing macrophages on histopathologic examinations,[4-6] and therefore they are considered to suggest the existence of a vulnerability of small blood vessels. In fact, CMBs have been described in association with a number of conditions reflecting the vulnerability of cerebral small vessels: an older age, hypertension, smoking, lacunar infarcts, prior ischemic strokes or intracranial hemorrhages, white matter disease, Alzheimer disease, and so on.[7] Several factors accelerating the occurrence of CMBs may overlap with the $CHADS_2$ score including advanced age, hypertension, and a past history of stroke. Therefore, a potential association between CMBs and the incidence of stroke in AF could be strongly speculated.

CMBs have been discussed only in relation to focal cerebrovascular disorders, and very little discussion has been reported in relation to AF. CMBs have been examined in cross-sectional studies,[8,9] and further, almost no long-term longitudinal observational studies targeting the variation in the CMBs have been performed. Moreover, CMBs have been discussed in patients with a previous history of stroke, because CMBs tend to be detected incidentally during diagnostic imaging for acute symptomatic strokes.

We hypothesized that CMBs and strokes share a common pathophysiology of microangiopathy in the context of AF. Therefore, an investigation in patients without a history of symptomatic stroke could be worthwhile to understand the genuine influence of CMBs. Under this hypothesis, we defined 2 goals in the present study: (1) to compare the evaluation of the prevalence of CMBs in patients with AF with that in patients without AF, and (2) to prove that CMBs could be a clinical predictive factor for the development of future cerebral microangiopathy in patients with AF without a history of symptomatic cerebral infarction in a prospective manner.

Materials and Methods

The entire study protocol was approved by the ethical review board of Asahikawa Medical University, and all patients gave their written informed consent for the present study.

Patient Enrollment and Cross-sectional Study

We performed a brain MRI assessment on the patients categorized into the following 2 groups: (1) AF subjects (Group AF): outpatients aged more than 45 with AF who visited the Cardiovascular, Respiratory, and Neurology Divisions of Asahikawa Medical University Hospital were consecutively enrolled. Patients with valvular AF or patients with any history of symptomatic cerebral infarction were excluded. (2) Control subjects (Group C): patients who underwent brain MRI scans for screening or diagnosing any neurologic disorders but without AF and any symptomatic cerebral infarction were enrolled.

Hypertension was defined as a systolic blood pressure greater than 140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg in subjects who were not taking antihypertensive medication, or continuously receiving antihypertensive treatment on an outpatient basis. Diabetes mellitus was defined by the Japan Diabetes Society as HbA1c value greater than 6.1 (corresponds approximately to the National Glycohemoglobin Standardization Program HbA1c value of >6.5) or any continuous antidiabetic treatment on an outpatient basis. Dyslipidemia was defined as a low-density lipoprotein cholesterol level greater than 140 mg/dL, a high-density lipoprotein cholesterol level less than 40 mg/dL, and/or a triglyceride level greater than 150 mg/dL, or continuously taking a cholesterol medication. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) level less than 60 mL/min/1.73 m^2 and/or overt albuminuria for more than 3 months continuously. Congestive heart failure was defined as that previously diagnosed by a cardiovascular specialist.

We compared the MRI findings in 2 groups, those with or without AF, especially in terms of the prevalence of CMBs. In addition, we compared the proportion of CMB occurrences according to the $CHADS_2$ score in Group AF.

Longitudinal Study

In Group AF of the cross-sectional study, yearly MRI scans were repeated with informed consent, and the time course of the above-documented variation in the CMBs (baseline CMBs), that is, whether there was an increase in the number or another cerebrovascular lesion such as cerebral infarction, was analyzed.

MRI Assessment

The MRI assessments were performed by trained observers who were blinded to the clinical information (J.S. and T.K.). We adopted the recommended criteria for the identification of CMBs proposed by Greenberg et al[2] to precisely assess the number of CMBs: (1) a black lesion on the T2*-weighted MRI; (2) round or ovoid lesions (rather than linear); (3) a blooming effect of the T2*-weighted MRI; (4) signals devoid of hyperintensity on the T1-weighted or T2-weighted sequences; (5) at least half of the lesion surrounded by brain parenchyma; (6) distinct from other potential mimicking conditions such