

Original Article

Changes in Serum Biochemical Markers in Relation to Chief Complaints and Aging in General Medicine

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To clarify potential relationships between chief complaints of patients and laboratory data with a focus on aging-related changes, we retrospectively analyzed the data of 843 patients who visited a general medicine department for the first time. Their chief complaints were classified into 8 major symptoms: visceral pain, somatic pain, fever, cough, dizziness, fatigue, appetite loss, and edema. We compared the laboratory data obtained from the patients with complaints with the data of symptom-free (control) patients. The serum sodium and potassium levels in the fever group were decreased compared to those in the control group. In the fever group, the serum sodium level was inversely correlated with age. The ratio of serum urea nitrogen to creatinine (UN/Cr) was increased in the appetite-loss group. There were significant age-dependent increases in the UN/Cr ratio in the appetite-loss and edema groups. Of note, serum levels of free thyroxin were lower in the dizziness group compared to the control group. In addition, the free thyroxin level was inversely correlated with age in the dizziness group but not in the asymptomatic control group. Collectively, the results indicated that osmolality-related laboratory data are strongly associated with individual primary symptoms at the first visit regardless of the final diagnosis. The consideration of age-dependent changes of these markers is helpful for diagnosing latent disorders based on various primary symptoms.

Key words: dizziness, fever, osmolality, serum sodium, thyroid dysfunction

The chief complaints of patients who visit a general medicine department for the first time to receive a medical examination are often diverse and complicated [1]. There have been several studies of the chief complaints reported in clinics in remote areas, in small and medium-sized hospitals, and in university hospitals [2-4]. In any medical situation, the representative complaints usually include cough, fever, headache and general fatigue, all of which are within the top 10 most common major complaints from patients. The process of reaching a diagnosis based on a patient's symptoms

involves a detailed medical interview, accurate physical examination, and various clinical workups including biochemical, physiological and radiological examinations [5]. There is a need for more rapid and more efficient approaches to achieve an accurate final diagnosis. We conducted the present study to clarify the potential inter-relationships between the main symptoms and laboratory data of patients' at their first visits to our university hospital department.

We focused on clinical markers related to the metabolism of water and electrolytes. Osmolality is determined by the concentrations of various solutes

contained in plasma or serum. In the absence of specific solutes in serum, a calculation using sodium salts, blood glucose, and urea nitrogen (UN) can be used to predict osmolality by the method of freezing-point depression [6-10]. We therefore used the patients' data of serum sodium, potassium, UN, and creatinine (Cr), the ratio of UN/Cr, and thyroid function (which are affected by the patient's metabolic balance of water and electrolytes) to determine the relationships between initial symptoms and laboratory results.

We did not use the patients' blood glucose levels in the present study since the effects of meals could not be avoided at the timing of the patients' visits to the hospital. To take into account the effects of aging, we also analyzed the patients' laboratory data with a focus on age-dependent changes. Our analyses revealed that taking into account age-dependent changes of osmolality-related markers could facilitate the diagnoses of latent disorders based on various primary symptoms.

Subjects and Methods

Study subjects. We retrospectively investigated the epidemiologic records of 1,540 patients who had visited the Department of General Medicine of Okayama University Hospital during the period from January 2012 to December 2012. Among those patients, 843 patients who underwent blood tests at their first visit were included in the present study. We divided the patients' cases into 10 groups based on their chief complaints, and we analyzed the inter-relationships between the patients' symptoms and their laboratory data. The no-symptom group included patients who were asymptomatic but had laboratory data abnormalities and/or lifestyle-related disease.

The data of each patient were also analyzed by a linear regression analysis with a focus on age. The patients included 358 males and 485 females (M/F: 0.74) with the mean age of 51.2 ± 19.1 years (mean \pm SD) and the age range of 15-91 years. Among the patients, 32.5% were <40 years old, 28.4% were 40-60 years old, and 35.5% were >60 years old. As shown in Table 1, the patients' final diagnoses included infection (15.8%), neuropsychiatric disease (13.2%), gastrointestinal disease (12.0%), metabolic and endocrine disorders (10.7%), orthopedic disease (5.1%), otolaryngology disease (4.9%), allergy and collagen disease (4.3%), cardiovascular disease (4.3%), urological and gynecological

Table 1 The patients' diagnoses

Final diagnosis	Number	%
Infection	133	15.8
Neuropsychiatric disease	111	13.2
Gastrointestinal disease	101	12.0
Metabo-Endocrine disorder	90	10.7
Orthopedic disease	43	5.1
Otolaryngology disease	41	4.9
Allergy-Collagen disease	36	4.3
Cardiovascular disease	36	4.3
Uro-Gynecology disease	29	3.4
Respiratory disease	28	3.3
Blood disease	24	2.8
Dermatological disease	13	1.5
Side effects of drugs	11	1.3
Unknown	147	17.4
Total	843	100

A total of 843 patients were classified into 14 groups based on their final diagnoses.

disease (3.4%), respiratory disease (3.3%), blood disease (2.8%), dermatological diseases (1.5%), side effects of drugs (1.3%), and unknown (17.4%).

Side effects of drugs occurred in 11 patients as follows: visceral pain (2 cases), fever (2 cases), cough (1 case), appetite loss (1 case), edema (1 case), and others (4 cases). The protocol of this study (K1612-020) was approved by the Institutional Review Board (IRB) of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

Laboratory examinations. The patients' blood cell counts, serum levels of electrolytes including sodium (Na) and potassium (K) and the serum levels of urea nitrogen (UN), creatinine (Cr), thyroid-stimulating hormone (TSH; thyrotropin), and free thyroxine (FT4) were determined by an auto-analyzer system in the Central Laboratory of Okayama University Hospital. The serum levels of TSH and FT4 were determined by an electrochemiluminescence immunoassay.

Statistical analysis. Results are shown as the mean \pm SEM of the data. The unpaired *t*-test and Kruskal-Wallis test were used to determine differences between the groups. If differences were detected by the Kruskal-Wallis test, the Steel-Dwass's post-hoc test was used to determine which means differed. A linear regression analysis and Spearman's rank correlation coefficients were also used to determine inter-relationships between the parameters. *P*-values <0.05 were

accepted as significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander (2.3-0) designed to add statistical functions frequently used in biostatistics [11].

Results

Chief complaints of the patients. The chief complaints of the patients are shown in Fig. 1. The patients were 358 males (42.5%) and 485 females (57.5%). The 10 main chief complaints of the patients were (1) somatic pain, (2) visceral pain, (3) fever, (4) cough, (5) dizziness, (6) fatigue, (7) appetite loss, (8) edema, (9) no symptoms, and (10) others. The numbers of patients with each complaint were as follows: somatic pain (n=169), visceral pain (n=132), fever (n=108), cough (n=83), dizziness (n=61), fatigue (n=56), appetite loss (n=34), edema (n=25), no symptoms (n=61), and others (n=114).

The most frequent chief complaint was pain, including both somatic pain and visceral pain (40.9% of the patients). The percentages of female patients were higher for the chief complaints of pain (59.5%), cough (56.6%), dizziness (59.0%), fatigue (64.3%), edema (64.0%), and appetite loss (52.9%). Based on their median age, the patients in the appetite loss group were mainly elderly individuals, whereas the majority of the fever-group patients were relatively young.

Relationships between electrolytes and the chief complaints. Fig. 2A shows the results of our comparison of serum sodium levels in the groups of the eight major complaints with those of the no-symptom group and the corresponding symptom-free groups. The serum sodium level in the fever group (n=108) was significantly lower than that in the fever-free group (n=735; $p < 0.05$). Fig. 2B illustrates the relationships between serum potassium levels and the major chief complaints. The serum potassium level in the fever group (n=108) was significantly lower than those in the fever-free group (n=735; $p < 0.01$) and the no-symptom group (n=68; $p < 0.05$). Age-dependent changes in serum sodium levels in the fever group and no-symptom group were analyzed. As shown in Fig. 2C, the serum sodium level had a significant inverse correlation

with age in the fever group (n=108; $R = -0.227$, $p < 0.05$) but not in the no-symptom group.

Relationships between the UN/Cr ratio and the chief complaints. Fig. 3A provides the results of our comparison of the UN-to-creatinine (UN/Cr) ratio in the eight major complaint groups with the no-symptom group and the corresponding symptom-free groups. The UN/Cr ratio in the fever group (n=107) was significantly lower than the ratios in the fever-free group (n=732; $p < 0.01$) and the no-symptom group (n=68; $p < 0.01$). In addition, the UN/Cr ratio in the cough group (n=83) was significantly lower compared to that in the no-symptom group (n=68; $p < 0.05$). The UN/Cr ratio in the appetite-loss group (n=34) was significantly higher than that in the symptom-free group (n=805; $p < 0.05$).

We also analyzed age-dependent changes in UN/Cr ratio values in the various groups. As shown in Fig. 3B, the UN/Cr ratio had significant correlations with age in the edema group (n=25; $R = 0.684$, $p < 0.01$) and the appetite-loss group (n=34; $R = 0.456$, $p < 0.01$) and also a weak correlation with age in the fever group (n=107; $R = 0.197$, $p < 0.05$), but the UN/Cr ratio had no correlation with age in the no-symptom group.

Relationships between thyroid function and the chief complaints. We compared aspects of thyroid function, including serum levels of thyrotropin (TSH) and free thyroxin (FT4), in the 8 major complaint groups with those in the no-symptom group and the corresponding symptom-free groups. Serum levels of TSH and FT4 were measured in 452 patients. As shown in Fig. 4A, the TSH levels in the patients with the eight major complaints were not significantly different from those in the symptom-free group and no-symptom group (n=41). The serum FT4 level was significantly lower in the dizziness group (n=35) compared to the symptom-free group (n=417; $p < 0.05$; Fig. 4B). As shown in Fig. 4C, the serum FT4 level had a significant inverse correlation with age in the dizziness group (n=35; $R = -0.469$, $p < 0.01$) but not in the no-symptom group.

Relationships between laboratory markers and final diagnoses. As shown in Fig. 5, the serum levels of Na and K, the UN/Cr ratio, and thyroid functions were analyzed in each disease group on the basis of the patients' final diagnosis. There was no particular distribution of these markers in the specific disorders or diseases that are listed as final diagnoses in Table 1. The

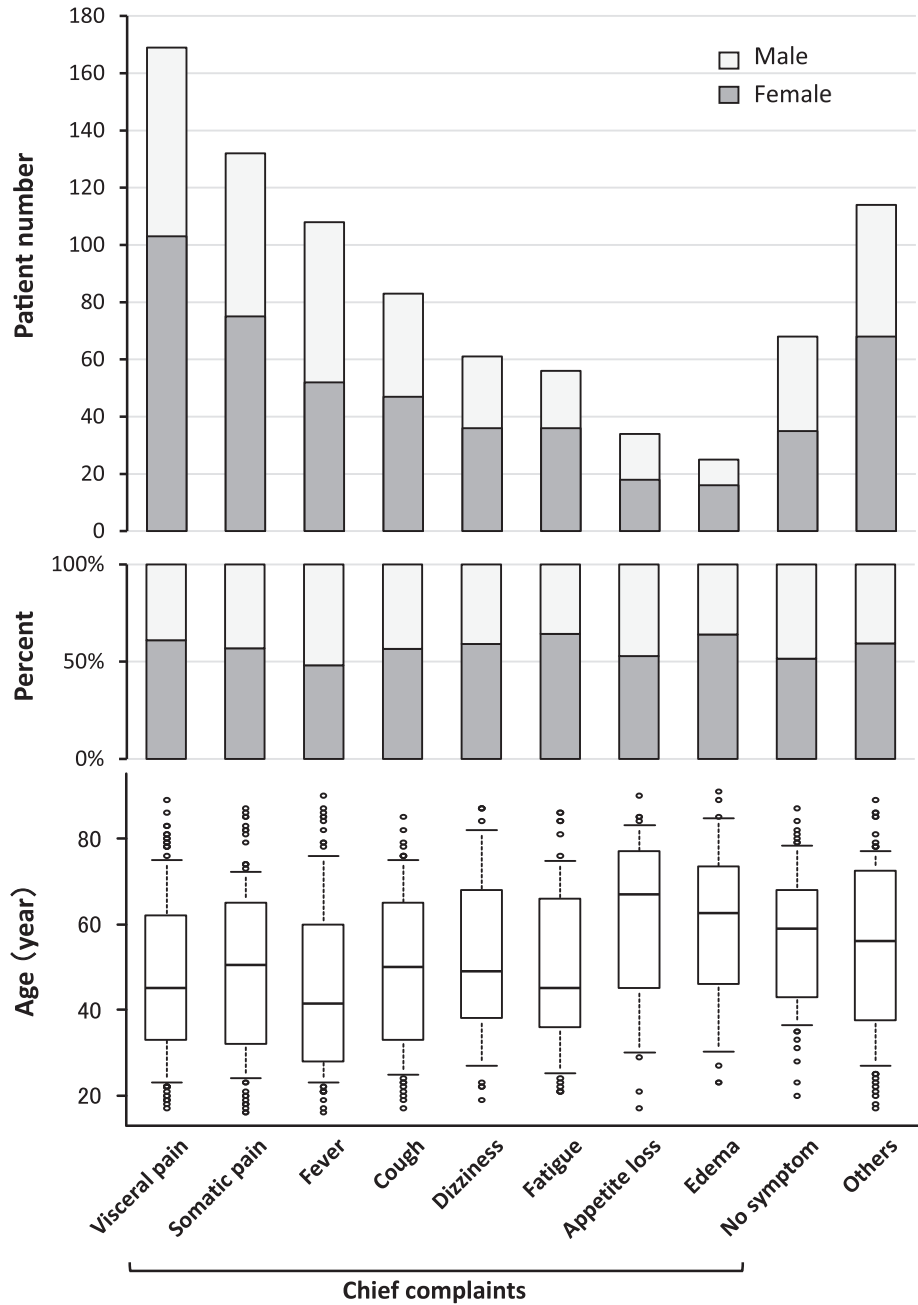


Fig. 1 The patients' chief complaints. We classified the 843 patients into 10 groups based on their chief complaints: visceral pain, somatic pain, fever, cough, dizziness, fatigue, appetite loss, edema, no symptoms, and others. *Middle panel*: the male-to-female ratios, and *lower panel*: the age distribution of each chief complaint. In the age distribution box plots: upper horizontal line of the box, 75th percentile; lower horizontal line of the box, 25th percentile; horizontal bar within the box, median; upper horizontal bar outside the box, 90th percentile; and lower horizontal bar outside the box, 10th percentile.

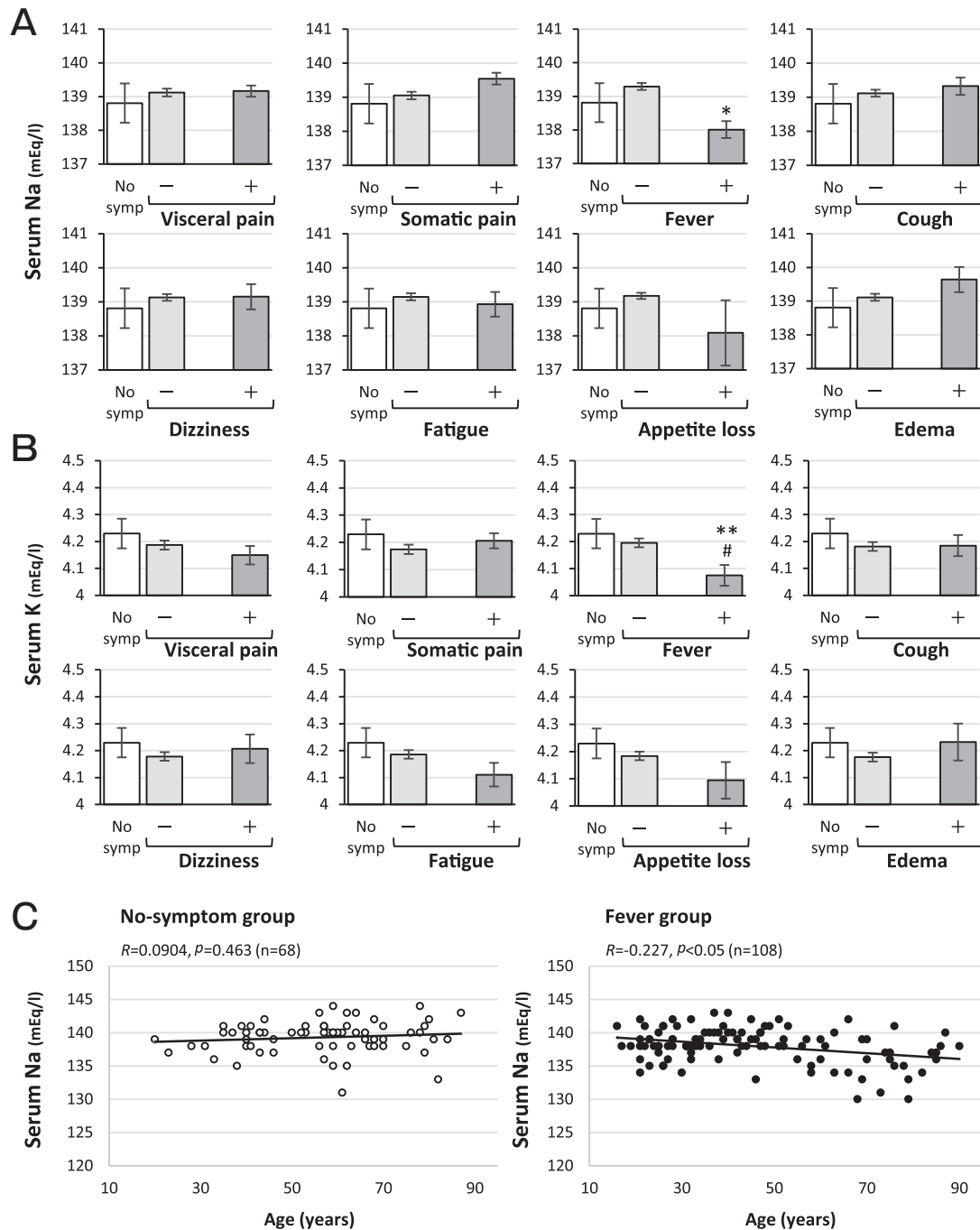


Fig. 2 Serum electrolyte levels in the 8 symptom-based groups and their age-related changes. Serum sodium (A) and potassium (B) levels were compared among the symptom-based groups of the 843 patients: no-symptom group (No symp, n = 68), visceral pain group (+, n = 169), somatic pain group (+, n = 132), fever group (+, n = 108), cough group (+, n = 83), dizziness group (+, n = 61), fatigue group (+, n = 56), appetite loss group (+, n = 34), and edema group (+, n = 25). Bars: mean \pm SEM of the data; unpaired *t*-test. **p* < 0.05, ***p* < 0.01 vs. corresponding symptom (-) groups; #*p* < 0.05 vs. no-symptom group. **C**: Relationships between serum sodium levels and age. The correlation between the serum sodium level and age was examined in a linear regression analysis.

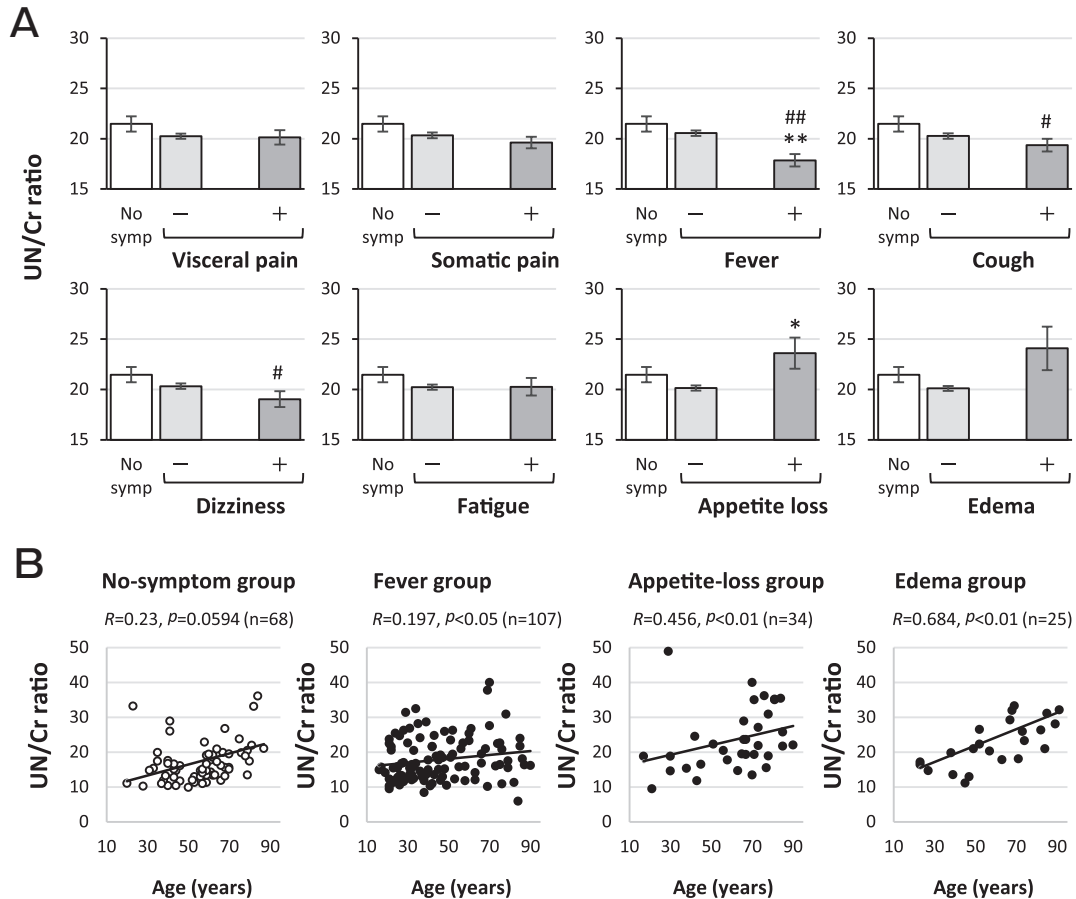


Fig. 3 The UN/Cr ratios in the symptom-based groups and their age-related changes. The ratio of the serum levels of UN to Cr (A) was compared among the eight symptom-based groups in the 839 patients: no-symptom group (No symp, n = 68), visceral pain group (+, n = 168), somatic pain group (+, n = 130), fever group (n = 107), cough group (+, n = 83), dizziness group (+, n = 61), fatigue group (+, n = 56), appetite loss group (+, n = 34), and edema group (+, n = 25). Bars: mean \pm SEM of the data; unpaired *t*-test. **p* < 0.05 and ***p* < 0.01 vs. corresponding symptom (-) groups; #*p* < 0.05, ##*p* < 0.01 vs. no-symptom group. **B**: Relationship between the UN/Cr ratio and age. The correlation between the serum sodium level and age was examined in a linear regression analysis.

serum levels of Na in the infection and metabo-endo disorder groups were lower than those in the otolaryngology group, whereas the UN/Cr ratio was lower in the infection group than in the groups of gastrointestinal, metabo-endo, allergy-collagen, cardiovascular, and respiratory diseases. Taken together, our results demonstrated that the serum Na level and the UN/Cr ratio were lower in the patients with infection as the final diagnosis.

Discussion

Because of the diversities of physical, mental, and social functions, there are various individual differ-

ences among elderly people, and complaints and findings are often atypical in many cases [12]. In the present study, we retrospectively analyzed clinical data including vital and physical signs and laboratory data for 843 outpatients who visited our department for the first time during a 1-year period. The patients were categorized by individual chief complaints based on our earlier classification [13,14], and we analyzed each parameter by focusing on age-related changes.

Our analyses revealed the following three major inter-relationships between the patients' chief complaints and biochemical markers even though the patients' final diagnoses diverged. (1) *Electrolytes*: The serum sodium and potassium levels were predomi-

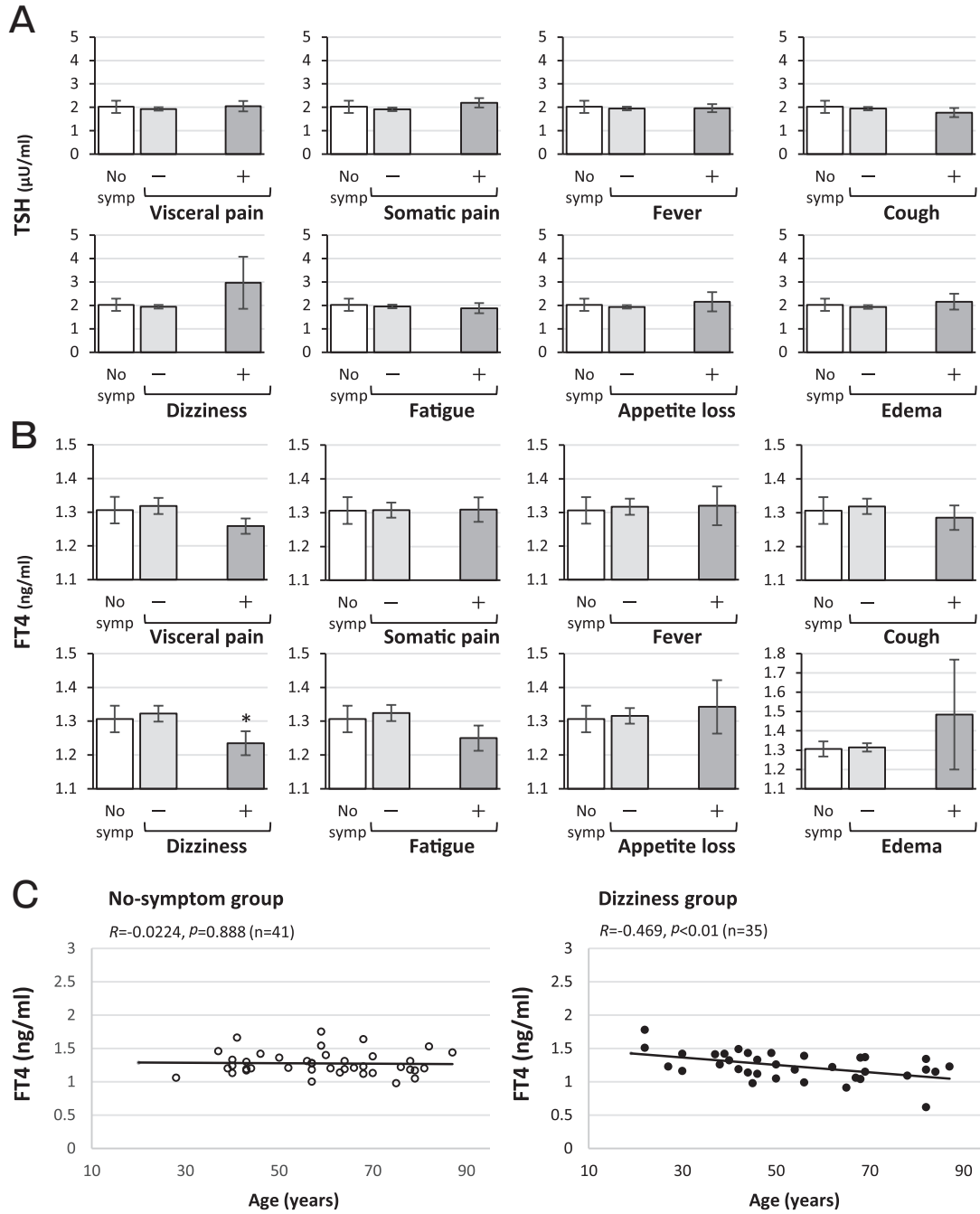


Fig. 4 Thyroid function in the symptom-based groups and their age-related changes. Serum levels of TSH (A) and FT4 (B) were compared among the eight symptom-based groups in 452 patients: no-symptom group (n = 41), visceral pain group (+, n = 83), somatic pain group (+, n = 51), fever group (n = 59), cough group (+, n = 25), dizziness group (+, n = 35), fatigue group (+, n = 43), appetite loss group (+, n = 29), and edema group (+, n = 16). Bars: mean ± SEM of the data; unpaired *t*-test. **p* < 0.05 vs. corresponding symptom (–) groups. **C**: Relationship between the serum FT4 level and age. The correlation between serum FT4 levels and age was examined in a linear regression analysis.

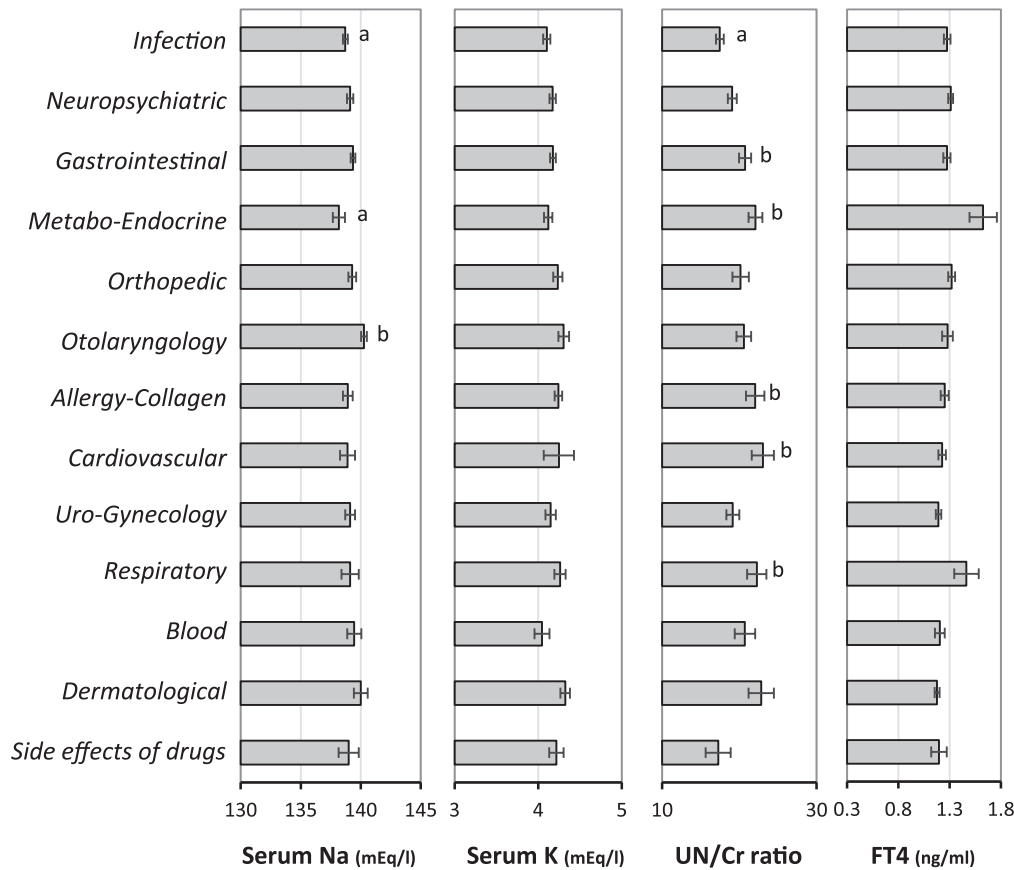


Fig. 5 Distributions of serum electrolytes, UN/Cr ratio, and thyroid function among the disease-based groups. The serum levels of Na and K, the UN/Cr ratio, and the serum level of FT4 were analyzed in each disease group based on the final diagnosis as shown in Table 1. Bars: mean \pm SEM of the data, by Kruskal-Wallis test. Values with different superscript letters are significantly different at $p < 0.05$.

nantly lower in the febrile group. Of note, the serum sodium levels tended to decrease in an age-dependent manner in the febrile patients. (2) *The UN/Cr ratio*: The UN/Cr ratio was decreased in the fever group, and increased in the appetite-loss group. The ratio of UN to Cr tended to increase with age, especially in the edema and appetite-loss groups. (3) *Thyroid functions*: Serum FT4 levels were lower in the dizziness group, and the serum FT4 levels tended to decrease age-dependently in the patients with dizziness. The serum TSH levels were not different among the symptom groups. Thus, regardless of the final diagnosis, attention must be paid to symptom-dependent and age-dependent changes in electrolytes and thyroid function.

Regarding the changes in serum electrolytes, we observed that the sodium and potassium levels were lower in the febrile patients. In addition, infection was a major cause of the decrease in serum sodium levels

among the diagnosis-based groups. Regarding the changes in serum sodium levels, an inverse relationship between the sodium level and febrile condition was shown previously [15], in which the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) leading to a sodium-losing condition seems likely to be induced.

Regarding the sodium balance in elderly people, the occurrence of mineralocorticoid-responsive hyponatremia of the elderly (MRHE) was described by Ishikawa *et al.* [16]. MRHE is thought to be a mild hypovolemic hyponatremia caused by sodium loss from the kidney. In the elderly, sodium reabsorption in renal tubules tends to be decreased, and the activity of the renin-angiotensin-aldosterone system also becomes blunted [17]. It is therefore possible that elderly people with fever may have an SIADH and/or an MRHE condition due to increased urinary sodium excretion [18].

Clinicians should pay attention to the fact that fever has a greater tendency to cause hyponatremia in elderly people compared to young people.

We observed that the UN/Cr ratio was also decreased in the fever group, but increased in the appetite-loss group. Among the diagnosis-based groups, infection was a relatively predominant cause of the decrease in the UN/Cr ratio. For each major complaint, the UN/Cr ratio tended to be increased with aging. The UN/Cr ratio in the edema group was more greatly age-dependently increased compared to those in the other groups. Since UN is produced by muscle destruction, it may increase as catabolism increases, such as in patients with appetite loss. Since urea excretion is greatly affected by renal blood flow, it increases with pre-renal factors such as dehydration and heart failure and, on the other hand, it declines in cases of polyuria.

It has been reported that the UN/Cr ratio increases with the use of diuretics, heart failure, renal failure, gastrointestinal bleeding, and decreased intravascular volume [19-22]. In the present study, there were eight patients who had taken diuretics, and another two patients were diagnosed as having a gastric ulcer. However, the increases in the UN/Cr ratio in the edema and appetite-loss groups might have been due mainly to their cardiac and/or renal insufficiency, especially in the elderly patients.

Our analyses demonstrated that the serum FT4 level was low in the patients who had a chief complaint of dizziness, and the FT4 level tended to have declined in the elderly patients. It has been reported that a decrease in the FT4 level due to aging is not recognized without any complaint [23, 24]. Regarding the relationships of thyroid dysfunction to aging, a higher prevalence of thyroid dysfunction has been shown in elderly populations [25, 26]. It was also reported that symptoms of hypothyroidism were hardly noticeable in the elderly [27]. Since hypothyroidism has been reported to be associated with Ménière's disease [28], elderly people may be prone to dizziness symptoms. In the present study, thyroid autoantibodies were measured in two patients in the dizziness group, and they were diagnosed as having hypothyroidism (an 82-year-old female) and Hashimoto disease (a 67-year-old female), suggesting that latent thyroid dysfunction may be associated with dizziness in elderly people.

Collectively, our results indicate clinical relevance between chief complaints and age-dependent changes in

biochemical markers. As our present findings were obtained using retrospective data from a university hospital, a multicenter study with a large population is necessary. In addition, medication bias on the laboratory data might have been unexpectedly included in this study. Our results study indicate that in elderly patients presenting with fever, appetite loss and/or edema, attention must be paid to their electrolyte levels and the UN/Cr ratio. Thyroid function might be lowered in patients with dizziness, and it is necessary to differentiate thyroid diseases in elderly patients with dizziness. The consideration of age-dependent changes in osmolality-related markers is helpful for diagnosing latent disorders in light of patients' various complaints when they visit a general medicine facility.

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