

Association between Serum Zinc Levels and Clinicopathological Characteristics in Patients with Gastric Cancer

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Keywords

Gastric cancer · Gastrectomy · Serum zinc · Nutritional indicator

Abstract

Introduction: Although it was reported that serum zinc levels were lower in patients with various malignancies, serum zinc levels of patients with gastric cancer were not well documented. **Objectives:** This study aimed to evaluate the association between clinicopathologic features and serum zinc levels in preoperative patients with gastric cancer. **Methods:** The study enrolled 83 patients scheduled for gastric cancer surgery at the Kochi Medical School. Clinical data were obtained to investigate associations between clinicopathological features, including nutritional indicators and serum zinc levels. Serum zinc deficiency was defined as serum zinc level <80 µg/dL. **Results:** The median zinc level of the 83 patients was 73 µg/dL (range, 20–152 µg/dL), and serum zinc deficiency was present in 66.3% of patients. Albumin was significantly lower in the zinc low level group than in the normal group (3.9 g/dL vs. 4.4 g/dL, $p < 0.001$), and the median serum zinc level was significantly lower in the albumin <4.1 g/dL

group than in the albumin ≥ 4.1 g/dL group (69 µg/dL vs. 82 µg/dL, $p < 0.001$). Lymphocyte count was significantly lower in the zinc low level group than in the normal group (1,500 vs. 1810 years, $p = 0.041$). The median serum zinc level was significantly lower in the age ≥ 74 group than in the age <74 (71 µg/dL vs. 76 µg/dL, $p = 0.002$). Serum zinc levels showed a significant positive correlation with serum albumin ($r = 0.637$, $p = 0.009$). **Conclusion:** Serum zinc deficiency was found in 66.3% of preoperative patients with gastric cancer, which was highly correlated with serum albumin.

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Introduction

Gastric cancer is a severe threat worldwide, is the fifth most common cancer and the third leading cause of cancer-associated death globally, and is the second most frequent cause of cancer-associated death in Japan [1, 2]. The nutritional status of patients with gastric cancer who require surgery for curative resection is deeply involved in

not only the postoperative course but also the patients' prognoses [3].

Excessive accumulation or depletion of trace elements may have significant clinical implications, including increased risk for cancer, cardiovascular disease, immune deficiency, anemia, renal function impairment, and bone disease [4]. Among the trace elements in the human body, zinc is the second most abundant, after iron only [5]. Zinc is an essential trace element for numerous biological processes including immune function, cell differentiation, and cell replication [6]. Serum deficiency of zinc is associated with various symptoms, such as diarrhea, dermatitis, chronic inflammation, alopecia, taste disorders, impaired wound healing, and boosting of the immune system [7].

Recent studies suggest that the increase or decrease of trace elements in the body may be related to the formation and development of many diseases, such as cancers, diabetes mellitus, and cardiovascular diseases [8, 9]. Because patients with gastric cancer have an impaired digestion due to involvement of the gastrointestinal tract with cancer, malnutrition is very common in these patients [10]. Therefore, nutritional deficiency of zinc has been associated with some deterioration in quality of life [11]. Although it was reported that serum zinc levels were lower in patients with various malignancies, serum zinc levels of patients with gastric cancer were not well documented [12].

So far, there are not many reports examining the relationships between gastric cancer and serum zinc levels, and there seems to be a lack of consensus among the results of existing reports [8]. The objective of the present study was to examine the incidence of serum zinc deficiency of patients with gastric cancer and evaluate the correlation between clinicopathological features, including the nutritional indicators of these patients and their serum zinc levels.

Materials and Methods

Study Participants

This study retrospectively reviewed the medical records of patients who were diagnosed with gastric cancer and scheduled for gastrectomy at Kochi Medical School. Gastric cancer diagnoses were determined by esophagogastroduodenoscopy, biopsy specimen analysis, computed tomography, magnetic resonance imaging, ultrasonography of the abdomen, and positron emission tomography. The participants visited the outpatient department of surgery to undergo gastrectomy for gastric cancer from December 2020 to February 2022. A total of 83 patients were referred.

Measurement of Variables

Patients' demographic data and clinicopathological characteristics, including height, body weight, and disease stage, were retrospectively collected from our institution's database. Body mass index (BMI) was calculated as weight (kg)/height (m)². Macroscopic type of the tumor was classified according to the classification system defined by the Japanese Gastric Cancer Association [13]. Tumor histology was categorized as intestinal type (well-differentiated, moderately differentiated, and papillary adenocarcinoma) or diffuse type (poorly differentiated, mucinous adenocarcinoma, and signet ring cell carcinoma) according to Lauren's classification. The exclusion criteria were: other types of cancer; other medical conditions known to affect anemia, including concurrent or previous hematology-related diseases; chronic kidney disease; and chronic liver disease.

Biochemical measurements were taken from peripheral blood samples collected during periodic follow-up physical examinations, including white blood cell count, albumin level, C-reactive protein (CRP), and serum levels of zinc. The neutrophil count divided by the lymphocyte count was recorded as neutrophil-to-lymphocyte ratio (NLR). Cutoff values for target serum variables were defined by the lower and upper limits of normal values set by the automatic biochemical detector used in our hospital for biochemical analysis. A serum zinc level under the cutoff value (80 µg/dL) was defined as a deficiency of serum zinc according to Japan's Practical Guidelines for Zinc Deficiency [14]. Blood antibody tests for *Helicobacter pylori* were performed to identify *H. pylori* infection. An electronic spirometer was used to measure respiratory function, and peak expiratory flow rate (PEFR), which was defined as the maximum flow rate that could be achieved by a forced expiratory maneuver and was assessed to evaluate respiratory sarcopenia [15].

This study was approved by the Institutional Review Board of Kochi Medical School, Kochi, Japan (Approval number: 2020-81) and was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Statistical Analysis

We tested for significant differences between mean values of the groups of patients using the Mann-Whitney U test for continuous variables and Pearson's χ^2 test for categorical variables. Statistical analyses were performed using SPSS for Windows, version 22.0.

Results

Patient Characteristics

Table 1 shows the clinical characteristics of the 83 patients who were diagnosed with gastric cancer. The study cohort was comprised of 53 men and 30 women, with a median age of 74 years and a median zinc level of 73 µg/dL. The median time interval between zinc examination and surgery was 22 days. Forty-three patients were diagnosed as having stage I gastric cancers and 23, 13, and 4 patients were found to have stage II, III, and IV disease, respectively. Median NLR was 2.37 (range, 0.73–28.68), and 35 patients (42.2%) were positive for serum *H. pylori* antibody.

Table 1. Clinical characteristics of the patients with gastric cancer

Variables	<i>n</i> = 83
Age, median (range), years	74 (43–89)
Sex	
Male	53
Female	30
Body mass index	22.2 (10.9–33.3)
Peak expiratory flow rate, L/sec	5.3 (1.4–9.5)
Time interval between zinc examination and surgery, median (range), days	22 (3–64)
Tumor location of gastric cancer	
Upper third of the stomach	16
Middle third of the stomach	32
Lower third of the stomach	29
Entire	6
Macroscopic type of gastric cancer	
Type 0	36
Type 1	6
Type 2	21
Type 3	13
Type 4	7
Pathology	
Intestinal type	46
Diffuse type	37
Disease stage	
I	43
II	23
III	13
IV	4
Serum <i>H. pylori</i> antibody	
Positive	35
Negative	48
Length of hospital stay, days	15 (8–158)
Zinc level, µg/dL	73 (20–152)
Neutrophil count, mm ³	3,805 (1,450–9,380)
Lymphocyte count, mm ³	1,600 (280–3,150)
Albumin, g/dL	4.1 (1.4–5.2)
C-reactive protein, mg/dL	0.12 (0.01–28.9)
Neutrophil-to-lymphocyte ratio	2.37 (0.73–28.68)

Clinical Characteristics of Patients Organized by Serum Zinc Levels

Serum zinc deficiency was present in 66.3% of the 83 patients. Table 2 summarizes the clinical characteristics of patients with gastric cancer organized by preoperative serum zinc levels. The median serum zinc level was 68 µg/dL (range, 20–79 µg/dL) in the low level group and 89 µg/dL (82–152 µg/dL) in the normal level group, with the difference being statistically significant ($p < 0.001$). Albumin was significantly lower in the zinc low level group than in the normal group (3.9 g/dL vs. 4.4 g/dL, $p < 0.001$). Lymphocyte count was significantly lower in the zinc low level group than in the normal group (1,500 vs. 1,810/mm³, $p = 0.041$). There were no significant differences

between the two groups in age, sex, BMI, PEFr, time interval between zinc examination and surgery, disease stage, NLR, neutrophil count, and CRP level.

Serum Zinc Levels of Patients Organized by Clinical Variables

Table 3 summarizes the serum zinc levels of patients with gastric cancer organized by clinical variables. Patients were divided into two groups based on the median value of each clinical variable as cutoff value. The median serum zinc level was 76 µg/dL (range, 38–152 µg/dL) in the patients who were less than 74 years of age and 71 µg/dL (20–93 µg/dL) in those who were more than 74 years of age, with the difference being statistically significant ($p = 0.002$). The median

Table 2. Clinical characteristics of patients with gastric cancer organized by preoperative serum zinc levels ($n = 83$)

Variable	Serum zinc level		<i>p</i> value
	low level $n = 55$	normal level $n = 28$	
Age, median (range), years	75 (47–89)	71 (43–87)	0.142
Sex			
Male	35	18	0.954
Female	20	10	
Body mass index	22.1 (10.9–33.3)	22.3 (14.9–28.4)	0.957
Peak expiratory flow rate, L/sec	5.2 (1.4–9.5)	5.6 (3.7–9.0)	0.367
Time interval between zinc examination and surgery, median (range), days	24 (3–62)	20 (8–64)	0.471
Disease stage			
I	27	16	0.932
II	17	6	
III	8	5	
IV	3	1	
Length of hospital stay, days	16 (11–158)	15 (8–158)	0.552
Zinc level, $\mu\text{g/dL}$	68 (20–79)	89 (82–152)	<0.001
Neutrophil count, mm^3	3,790 (1,450–8,030)	3,870 (1,780–9,380)	0.864
Lymphocyte count, mm^3	1,500 (280–3,150)	1,810 (820–2,700)	0.041
Albumin, g/dL	3.9 (1.4–4.6)	4.4 (2.7–5.2)	<0.001
C-reactive protein, mg/dL	0.14 (0.02–28.9)	0.08 (0.01–3.14)	0.152
Neutrophil-to-lymphocyte ratio	2.67 (0.73–28.68)	1.97 (0.91–7.50)	0.198

serum zinc level was also significantly lower in the patients with serum albumin <4.1 g/dL than in those with serum albumin ≥ 4.1 (69 vs. 82 $\mu\text{g/dL}$, $p < 0.001$). The median serum zinc level was significantly higher in the patients with NLR <2.37 than in those with NLR ≥ 2.37 (75 vs. 72.5, $p = 0.012$). There were no significant differences between the two groups in sex, BMI, disease stage, PEFr, time interval between zinc examination and surgery, *H. pylori* infection status, neutrophil count, lymphocyte count, and CRP.

Relationship between Serum Zinc Level and Patient Characteristics

Figures 1–3 show the correlations between serum zinc levels and patient characteristics. Serum zinc levels showed positive correlation with serum albumin ($r = 0.637$, $p = 0.009$; Fig. 1) and lymphocyte count ($r = 0.295$, $p = 0.330$; Fig. 2). There was a negative correlation between the serum zinc level and age ($r = -0.361$, $p = 0.221$; Fig. 3).

Discussion

We found that serum zinc deficiency was present in 66.3% of the patients who were scheduled for gastrectomy for gastric cancer, and the serum level of zinc in patients with gastric cancer was significantly associated with serum albumin levels and lymphocyte count. To the best of our

knowledge, for the first time, the results of this study indicate that the serum level of zinc had an association with the lymphocyte count of the patients with gastric cancer.

Henderson et al. [16] reported that zinc is practically insoluble at a high intragastric pH, and the dissolution of zinc at this pH is extremely low. Thus, in the absence of gastric acidity, zinc would not be expected to dissolve well in the stomach or intestine; therefore, zinc would not be well absorbed. Patients with gastric cancer usually have advanced precancerous changes in gastric mucosa, including glandular atrophy and intestinal metaplasia, on histologic analysis [17]. The clinical manifestation, such as gastric mucosal atrophy or intestinal metaplasia, involves low stomach acid, resulting in high pH in the digestive tract. Sempértegui et al. reported that *H. pylori* infection is correlated with a significant reduction in the concentration of zinc in the gastric mucosa of patients [18]. Inclusion of zinc supplementation may become part of the treatment protocol during perioperative management for patients with gastric cancer because zinc deficiency is negatively associated with wound healing and boosting of the immune system [19].

Chen et al. [20] reported that dietary zinc deficiency can inhibit growth and promote the proliferation of esophageal epithelial squamous cells in mice, a mechanism which may be related to induced tumor-related factors such as over-expression of predictive

Table 3. Serum zinc levels of patients with gastric cancer organized by clinical variables

Variable	Serum zinc level, $\mu\text{g/dL}$	<i>p</i> value
Age		
<74 years	76 (38–152)	0.002
≥ 74 years	71 (20–93)	
Sex		
Male	74 (43–152)	0.524
Female	71 (20–135)	
Body mass index		
<22.2	72 (20–152)	0.311
≥ 22.2	75 (43–133)	
Peak expiratory flow rate, L/sec		
<5.3	72 (20–135)	0.419
≥ 5.3	73 (47–152)	
Serum <i>H. pylori</i> antibody		
Positive	72 (48–133)	0.704
Negative	75 (20–152)	
Neutrophil count, mm^3		
<3,805	73 (38–152)	0.957
$\geq 3,805$	73 (20–133)	
Lymphocyte count, mm^3		
<1,600	73 (20–135)	0.086
$\geq 1,600$	74 (47–152)	
Albumin, g/dL		
<4.1	69 (20–135)	<0.001
≥ 4.1	82 (48–152)	
C-reactive protein, mg/dL		
<0.12	77 (43–135)	0.100
≥ 0.12	72 (20–152)	
Neutrophil-to-lymphocyte ratio		
< 2.37	75 (43–152)	0.012
≥ 2.37	72.5 (20–99)	

biomarkers, including COX-2, P38, PCNA, and NF- κ B. On the other hand, Zhang et al. [21] did not support a significant association between serum zinc level and colorectal cancer risk in the general US population through the use of the National Health and Nutrition Examination Survey (NHANES) 2011–2016 data. Because of these controversial results, the possible role of trace elements in the initiation or inhibition of cancer is still not fully understood; therefore, further studies are needed to determine possible mechanisms of the carcinogenesis.

Although limited information indicates that zinc status is associated with gastric cancer, a recent study showed that serum zinc deficiency was found in 68.6% of 617 postoperative patients who underwent gastrectomy for gastric cancer [5]. Furthermore, Hagi et al. [22] reported that patients with a decreased sweet sensitivity had lower serum zinc concentrations than those without it in a study of the postoperative

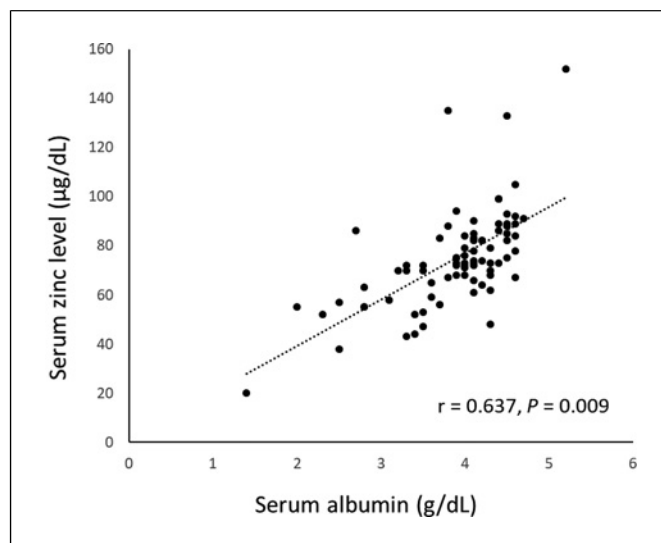


Fig. 1. Scatter plot of serum zinc levels compared to serum albumin. Significant positive correlation is observed between serum zinc level and serum albumin ($r = 0.637$, $p = 0.009$).

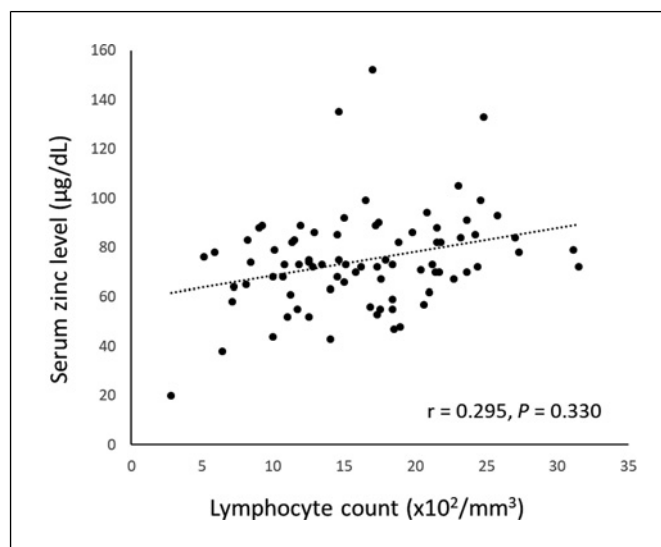


Fig. 2. Scatter plot of serum zinc levels compared to lymphocyte count. Positive correlation is observed between serum zinc level and lymphocyte count ($r = 0.295$, $p = 0.330$).

evaluation of 243 patients with gastric cancer, while symptoms of zinc deficiency varied depending on its severity. Due to a deficiency of serum zinc in patients with gastric cancer, in addition to post-gastrectomy status, suitable nutritional interventions including trace elements should be assessed to maintain immune system function, taste function, and wound healing processes in these patients.

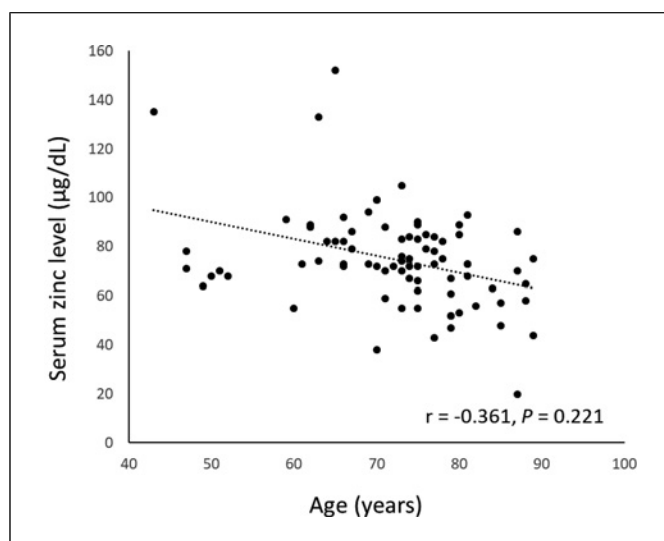


Fig. 3. Scatter plot of serum zinc levels compared to age. Positive correlation is observed between serum zinc level and age ($r = -0.361$, $p = 0.221$).

This study also found that there was a significant positive correlation between serum zinc levels and serum albumin and lymphocyte count. Previous studies demonstrated a statistical correlation between zinc and albumin in both healthy participants and patients who underwent gastrectomy for gastric cancer [4, 5]. The majority of plasma zinc is bound to serum albumin because serum albumin acts as a transport protein [23, 24]. Moreover, it has been reported that sarcopenia, which is a degenerative muscle disease or muscle failure, is associated with multifactorial causes, including nutritional status and reduced peak expiratory flow, increasing mortality rates, and functional decline [25, 26]. Therefore, zinc deficiency status associated with malnutrition in patients with cancer might be involved in poor prognosis. Further investigations of the relationship between zinc levels and cancer-bearing condition, including cytokines and immune function indicators, are needed to explain the role of zinc in health and diseases.

The present study demonstrated that the median serum zinc level was significantly higher in the patients with NLR <2.37 than in those with NLR ≥ 2.37 . Circulating lymphocytes play an important immunological role in various carcinomas, while neutrophilia as an inflammatory response inhibits the immune system [27]. Several investigators have also reported that zinc deficiency leads to impaired immune function in zinc-deficient participants utilizing an experimental model of human

zinc deficiency [28–33]. Accordingly, it is conceivable that zinc deficiency results in immune dysfunction and promotes systemic inflammation. The balance between the immune reactivity and host inflammatory response may have a significant role in the development and progression of cancer [3].

The present study also has several potential limitations. First, this study was based on a retrospective analysis in a single institution, so several confounders and selection bias might have influenced the study results. Second, the sample size of the present study was not large enough, which might make the results of this study less convincing. Third, we did not consider underlying diseases that might have influenced the concentrations of trace elements, such as metabolic and endocrine disorders, neurological disorders, and infectious causes. Consequently, larger prospective multicenter studies with adequate statistical power are warranted to validate our findings.

Conclusion

The incidence of zinc deficiency is high in patients with gastric cancer, and it was observed that the serum level of zinc had an association with the serum albumin level and lymphocyte count. Further studies are still required to confirm and update our results and to establish more intensive pharmacologic interventions for patients with gastric cancer.

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Statement of Ethics

All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study protocol was reviewed and approved by the Institutional Review Board of Kochi Medical School, Kochi, Japan, approval number, 2020-81, and was conducted according to the principles of the Declaration of Helsinki. Written informed consent for participation was obtained from all patients in this study.

Conflict of Interest Statement

All authors declare that they have no conflict of interest.

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Michiya Kobayashi: acquisition of data; Tsutomu Namikawa and Hiromichi Maeda: analysis and interpretation of data; Tsutomu Namikawa and Kazuhiro Hanazaki: critical revision of manuscript.

Author Contributions

Tsutomu Namikawa: study conception, drafting of manuscript, and design; Tsutomu Namikawa, Masato Utsunomiya, Keiichiro Yokota, Masaya Munekage, Sunao Uemura, Hiroyuki Kitagawa, and

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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