Factors associated with other-cause survival after gastrectomy in patients with gastric cancer

Ryota Matsui (supreme0818@gmail.com)
Ishikawa Prefectural Central Hospital
Noriyuki Inaki
Ishikawa Prefectural Central Hospital
Toshikatsu Tsuji
Ishikawa Prefectural Central Hospital

Research Article

Keywords: body composition, gastric cancer, malnutrition, other-cause survival, prognosis

Posted Date: May 18th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1636316/v1

Abstract

Purpose: Death due to other diseases is one factor related to long-term prognosis after gastrectomy; however, few studies have examined the relationship between death due to other diseases and undernutrition. This study aimed to clarify the factors associated with death due to other diseases after gastrectomy for gastric cancer.

Methods: This retrospective cohort study included consecutive patients who had undergone gastrectomy between April 2008 and June 2018 for primary stage II–III gastric cancer. The primary outcome was other-cause survival (OCS). To identify prognostic factors for OCS for univariate analysis, we used a Cox proportional hazards regression model.

Results: A total of 512 patients met the inclusion criteria. The average age was 67.93 years, and the average body mass index was 22.75 kg/m^2, with 84 (16.4%) moderately malnourished and 88 (17.2%) severely malnourished, as defined by the Global Leadership Initiative on Malnutrition (GLIM) criteria. The OCS for the malnourished group was significantly worse than that for the normal group ($P < 0.001$). The prognosis was worse when the severity of malnutrition was worse ($P < 0.001$). Multivariate analysis showed that severe malnutrition (hazard ratio [HR]: 3.259, 95% confidence interval [CI]: 1.396–7.609, $P = 0.006$) and severe postoperative complications (HR: 4.245, 95% CI: 2.207–8.166, $P < 0.001$) were significant independent prognostic factors for OCS.

Conclusions: Undernutrition, as defined by the GLIM criteria, is useful for the preoperative prediction of death due to other diseases after gastrectomy in patients with advanced gastric cancer.

Introduction

Recently, body composition, including skeletal muscle mass and fat mass, has been used to assess undernutrition, and its correlation with the prognosis for patients with gastric cancer after gastrectomy has been explored. The widely accepted Global Leadership Initiative on Malnutrition (GLIM) criteria considers reduced muscle mass to be indicative of undernutrition, suggesting that patients with sarcopenia are undernourished [1]. A recent systematic review has shown that reduced skeletal muscle mass is associated with a poor prognosis for gastric cancer patients [2], and reduced visceral and subcutaneous fat mass is also associated with a poor prognosis for gastric cancer patients [3, 4]. Therefore, the assessment of body composition is essential for predicting postoperative outcomes.

Death due to other diseases is one factor related to long-term prognosis after gastrectomy; however, few studies have examined the relationship between death due to other diseases and undernutrition. Sarcopenia has been reported to increase short-term postoperative pneumonia [5]. In addition, the preoperative assessment of muscle quantity and quality, in particular, has been reported to be useful in assessing long-term death due to other diseases [6]. However, the effect of visceral and subcutaneous fat on death due to other diseases has not been clarified, and the relationship between undernutrition and death due to other diseases, as defined by the GLIM criteria, has not been fully investigated. The preoperative prediction of death due to other diseases after gastrectomy is an important factor in postoperative treatment and its selection.

This study aimed to clarify the factors associated with death due to other diseases after gastrectomy for advanced gastric cancer. In addition to cancer-related and surgical factors, we focused on body composition and undernutrition as defined by the GLIM criteria, which have recently attracted attention.

Material And Methods

Patients

This retrospective cohort study included consecutive patients who had undergone a gastrectomy between April 2008 and June 2018 for primary stage II–III gastric cancer, as defined by the 15th edition of the Japanese Classification of Gastric Carcinomas. Patients were excluded if they (1) had residual gastric cancer, (2) had cancer in other organs, (3) had undergone surgical procedures not related to gastrectomy, (4) had unresectable distant metastases, and (5) had undergone preoperative treatment. Patients with positive ascites cytology (CY1) without distant metastases were included. The Institutional Ethical Review Committee of Ishikawa Prefectural Central Hospital approved the study protocol (authorization No. 1847).

Outcomes

Other-cause survival (OCS), defined as the time between surgery and death not related to the gastric cancer, was the primary outcome of this study. Kaplan-Meier survival analysis was performed using the log-rank test for OCS. To identify prognostic factors for OCS for univariate analysis, we used a Cox proportional hazards regression model, in which multivariate analysis was conducted to obtain hazard ratios (HRs). Statistical analyses were performed using EZR software and statistical significance was set at $P < 0.05$.

Definition of other factors

The GLIM criteria were used in this study to define the parameters used to diagnose the severity of malnutrition [1]. The body mass index (BMI) and body weight loss (BWL) rate were used to classify the patients as having moderate or severe malnutrition, according to the GLIM criteria (Table 1). Normal nutrition was defined as the absence of malnutrition.

Visual analysis of preoperative plain computed tomography (CT) images using the graphical analysis software Ziostation (ZIOSOFT, Tokyo, Japan) was used to estimate visceral and subcutaneous fat mass at the umbilical level, as well as skeletal muscle mass at the third lumbar vertebra level. Visceral and subcutaneous fat mass and skeletal muscle mass were measured on one CT image slice. The masses were divided by the height of the patient to determine the visceral adipose tissue index (VAI), subcutaneous adipose tissue index (SAI), and skeletal muscle mass index (SMI), respectively. As performed in previous studies, we measured the CT values (in Hounsfield units [HU]) of the regions of interest at the umbilical level and then calculated the intramuscular adipose tissue content (IMAC) by dividing the CT value of the multifidus muscles by the CT value of the subcutaneous fat [7]. The cutoff values for the VAI, SAI, and IMAC were estimated for men and women based on the median values for each group, and the reported cutoff values for SMI were adopted [8]. The cutoff values for each parameter are presented in Table 2. Patients with an SMI below or above the cutoff value were classified as having a low SMI or a high SMI, respectively. Low SMI was further divided into moderate and severe SMI [8].

We defined postoperative complications that occurred within 30 days after surgery as Clavien-Dindo classification (CD) grade ≥ 2 and severe complications as CD grade ≥ 3.

Results

Patient background

Table 3 presents a summary of patient characteristics. A total of 512 patients [336 (65.6%) male and 176 (34.4%) female] met the eligibility criteria. The average age was 67.93 years and the average BMI was 22.75 kg/m^2. The pathological stages of the patients were as follows: 88 (17.2%) were stage I, 176 (34.4%) were stage II, 193 (37.2%) were stage III, and 55 (10.7%) were stage IV. Eighty-four (16.4%) patients were moderately malnourished and 88 (17.2%) were severely malnourished. The low-SMI group comprised 235 (48.5%) patients, while the moderate and severe groups comprised 152 (31.3%) and 83 (17.1%), respectively. There were 246 (50.7%) in the high-IMAC group, 243 (50.1%) in the low-VAI group, and 242 (49.9%) in the low-SAI group.

Comparison of OCS curves

Death due to other diseases was observed in 45 (8.8%) patients. The median follow-up time was 41 months (interquartile range: 17–60 months). The OCS curves of the two groups are compared in Fig. 1. The prognosis for the malnourished group was significantly worse than that for the normal group (P< 0.001), that for the low-SMI group was significantly worse than that for the high-SMI group (P= 0.003), and that for the low-SAI group was significantly worse than that for the high-SAI group (P= 0.001). In contrast, the prognoses for the high- and low-IMAC groups (P= 0.476) and the low- and high-VAI groups were not significantly different (P= 0.076).

Stratified survival curves for OCS

The stratified survival curves for OCS are shown in Fig. 2. As can be seen from Fig. 2a, the prognosis worsened with increasing severity of malnutrition(P< 0.001). Figure 2b shows that both moderate and severe low-SMI patients had a poor prognosis (P= 0.006). Figure 2c shows that patients with the comorbidities of low SMI and high IMAC had the worst prognosis (P= 0.036). Finally, Fig. 2d shows that the patients with both low VAI and low SAI had the worst prognosis (P= 0.015).

Prognostic factors for OCS

Table 4 presents the results of the analysis of the prognostic factors for OCS. Univariate analysis showed that age ≥ 70 years ($P < 0.001$), D2 lymph node dissection ($P = 0.038$), moderate and severe malnutrition ($P = 0.013$ and $P < 0.001$, respectively), severe low SMI ($P = 0.024$), low SAI ($P = 0.002$), and severe postoperative complications ($P < 0.001$) were statistically significant prognostic factors for OCS. Multivariate analysis showed that age ≥ 70 years (HR: 2.450, 95% confidence interval [CI]: 1.219–4.927, $P = 0.012$), severe malnutrition (HR: 3.259, 95% CI: 1.396–7.609, $P = 0.006$), and severe postoperative complications (HR: 4.245, 95% CI: 2.207–8.166, $P < 0.001$) were significant independent prognostic factors for OCS.

Discussion

Our study identified factors associated with death due to other diseases after gastrectomy in patients with advanced gastric cancer. We found that severe malnutrition, as defined by the GLIM criteria and assessed by BMI and BWL, as a preoperative predictor and the occurrence of severe complications with CD grade 3 or higher as a postoperative factor were independent factors associated with a poor prognosis for OCS.

In this study, pneumonia was the most common cause of death among the other diseases. GLIM-defined malnutrition has been linked to death due to other diseases caused by pneumonia, which is a complication of gastric cancer and the risk of which increases as undernutrition increases [8]. In addition, severe GLIM-defined undernutrition not only increases postoperative pneumonia but also increases mortality within 90 days after surgery [9]. The present study showed that severe GLIM-defined undernutrition increases the incidence of fatal pneumonia in the long term. This is the first study to show that GLIM-defined undernutrition is a factor associated with a poor prognosis for OCS.

Analysis of body composition revealed that muscle quantity, muscle quality, visceral fat mass, and subcutaneous fat mass were not independent indicators of OCS. Comparison of the survival curves showed that the comorbidities of low SMI and high IMAC were factors for a poor prognosis, as were low VAI and low SAI. A previous report showed the usefulness of the assessment of muscle quantity and quality in predicting death due to other diseases [6], supporting the results of this study. We used the SMI cutoff value, which is the most commonly used value in Asia, and further divided the low-SMI category into moderate and severe SMI, but neither factor was an independent predictor of a poor prognosis. Based on these results, the combination of muscle mass and muscle quality is more useful than muscle mass and muscle quality separately for predicting the prognosis for OCS. The assessment of handgrip strength has been regarded essential for the diagnosis of sarcopenia [10]. In an earlier study, we showed that low preoperative handgrip strength increases the risk of death due to other diseases [11]. In addition to muscle mass and muscle quality measurements, functional assessments may be useful in predicting death due to other diseases, but further study is needed. Although fat mass reflects excessive nutrient accumulation, BWL occurs after gastrectomy. Those with low VAI and low SAI before gastrectomy may experience postoperative energy depletion. This suggests that body composition assessment alone cannot predict death due to other diseases.

Regarding the generalization of our results, determination of GLIM-defined malnutrition based on BMI and BWL does not require any special tests and can be easily performed immediately in daily clinical practice. In addition, GLIM-defined malnutrition can be evaluated repeatedly, not only preoperatively, but also during the follow-up period. In this study, we did not include low SMI in the diagnosis of GLIM-defined malnutrition because the cutoff value for muscle mass has not been established in the current GLIM criteria, so its validity has not been verified. Multivariate analysis suggested that GLIM-defined malnutrition based on BMI and BWL may be more useful than muscle mass alone in predicting death due to other diseases.

This study has some limitations. First, it was a single-center retrospective cohort study. Second, the cutoff values of the parameters are unclear and require validation by additional multicenter cohort studies. This study revealed that a low preoperative BMI or a high BWL may increase the risk of death due to other diseases in gastric cancer patients with postoperative weight loss. Patients with preoperative GLIM-defined malnutrition should be followed up to check their nutritional status and, if necessary, considered for nutritional support. They should also be followed up for any postoperative decline in physical function. Intervention with physical exercise may be necessary to prevent long-term pneumonia and muscle weakness due to lack of use. Therefore, it is necessary to clarify whether such nutritional and exercise interventions have prolonged prognostic effects on patients with GLIM-defined malnutrition.

Conclusion

undernutrition as defined by the GLIM criteria is useful for the preoperative prediction of death due to other diseases after gastrectomy in patients with advanced gastric cancer.

Declarations

Acknowledgments: Not applicable.

Conflict of interest: The authors have no conflicts of interest to declare.

Funding statement: This research did not receive any grants from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement: The study protocol was approved by the Institutional Ethical Review Committee of Ishikawa Prefectural Central Hospital (authorization No. 1847).

Statement of informed consent: Informed consent was obtained from all individual participants included in the study.

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions: R. Matsui and N. Inaki contributed equally to the conception and design of the research. R. Matsui and T. Tsuji contributed to the acquisition and analysis of the data. R. Matsui and N. Inaki contributed to the interpretation of the data. R. Matsui and N. Inaki drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References

1. Cederholm T, Jensen GL, Correia MITD, Gonzalez MC, Fukushima R, Higashiguchi T, et al; GLIM Core Leadership Committee; GLIM Working Group (2019) GLIM criteria for the diagnosis of malnutrition - a consensus report from the global clinical nutrition community. Clin Nutr 38:1–9.
2. Rinninella E, Cintoni M, Raoul P, Pozzo C, Strippoli A, Bria E, et al (2020) Muscle mass, assessed at diagnosis by L3-CT scan as a prognostic marker of clinical outcomes in patients with gastric cancer: A systematic review and meta-analysis. Clin Nutr 39:2045–54.
3. Matsui R, Inaki N, Tsuji T (2021) Impact of visceral adipose tissue on compliance of adjuvant chemotherapy and relapse-free survival after gastrectomy for gastric cancer: A propensity score matching analysis. Clin Nutr 40:2745–53.
4. Li XT, Tang L, Chen Y, Li YL, Zhang XP, Sun YS (2015) Visceral and subcutaneous fat as new independent predictive factors of survival in locally advanced gastric carcinoma patients treated with neo-adjuvant chemotherapy. J Cancer Res Clin Oncol 141:1237–47.
5. Yang Z, Zhou X, Ma B, Xing Y, Jiang X, Wang Z (2018) Predictive value of preoperative sarcopenia in patients with gastric cancer: a meta-analysis and systematic review. J Gastrointest Surg 22:1890–902.
6. Watanabe J, Osaki T, Ueyama T, Koyama M, Iki M, Endo K, et al (2021) The combination of preoperative skeletal muscle quantity and quality is an important indicator of survival in elderly patients undergoing curative gastrectomy for gastric cancer. World J Surg 45:2868–77.
7. Matsui R, Inaki N, Tsuji T (2021) Impact of preoperative muscle quality on postoperative severe complications after radical gastrectomy for gastric cancer patients. Ann Gastroenterol Surg 5:510–8.
8. Xu LB, Shi MM, Huang ZX, Zhang WT, Zhang HH, Shen X, et al (2021) Impact of malnutrition diagnosed using Global Leadership Initiative on Malnutrition criteria on clinical outcomes of patients with gastric cancer. JPEN J Parenter Enteral Nutr. doi: 10.1002/jpen.2127.
9. Kakavas S, Karayiannis D, Bouloubasi Z, Poulia KA, Kompogiorgas S, Konstantinou D, et al (2020) Global Leadership Initiative on Malnutrition criteria predict pulmonary complications and 90-day mortality after major abdominal surgery in cancer patients. Nutrients 12:3726.
10. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2 (2019) Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48:16–31.

11. Matsui R, Inaki N, Tsuji T (2021) The impact of the preoperative hand grip strength on the long-term outcomes after gastrectomy for advanced gastric cancer. Surg Today 51:1179–87.

Tables

Tables 1-4 are not available with this version.

Figures

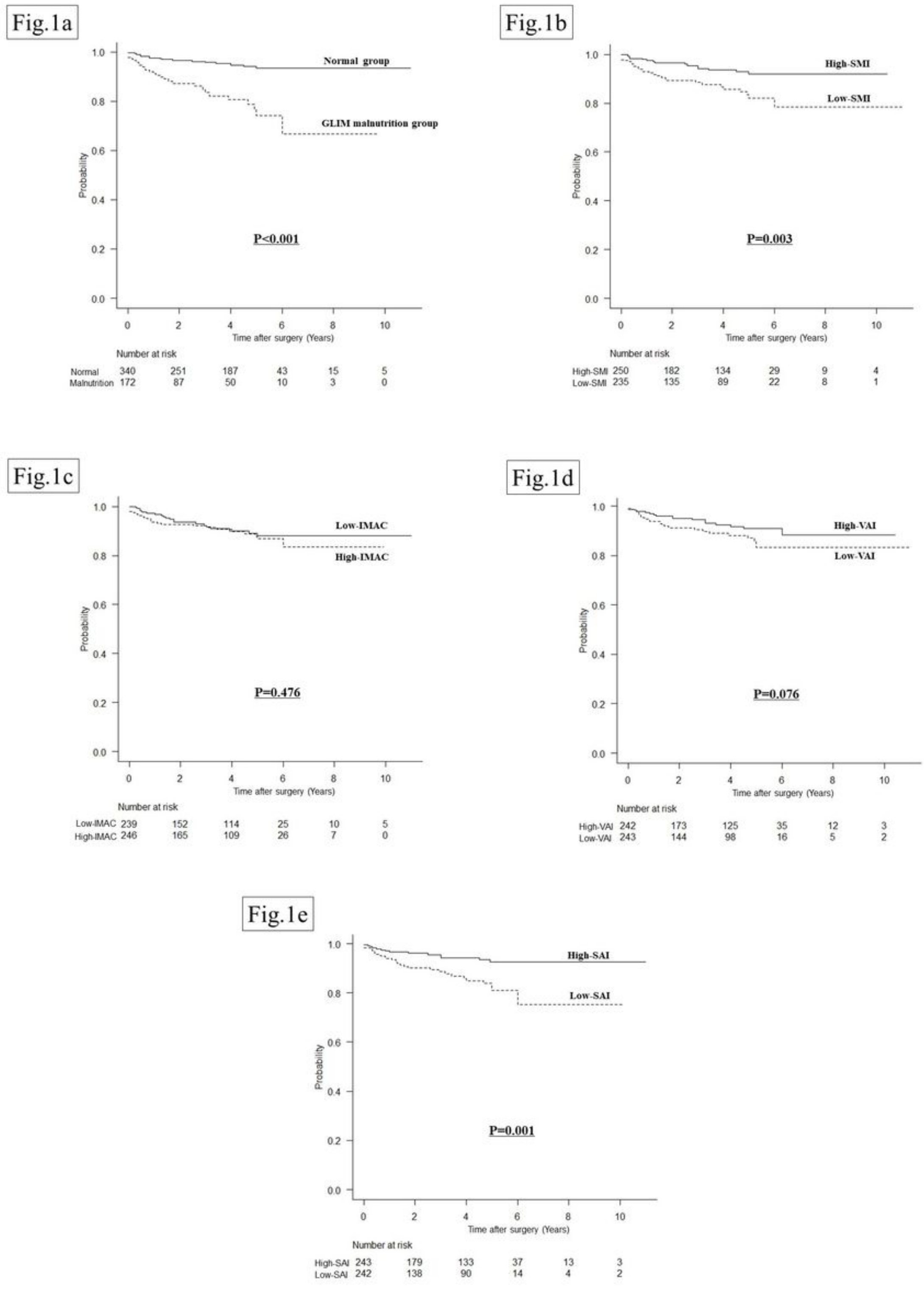

Figure 1

Other-cause survival curves with respect to the following factors:

(a) malnutrition defined by GLIM criteria ($P < 0.001$),

(b) SMI ($P = 0.003$),

(c) IMAC (P = 0.476),

(d) VAI (P = 0.076),

(e) SAI (P = 0.001).

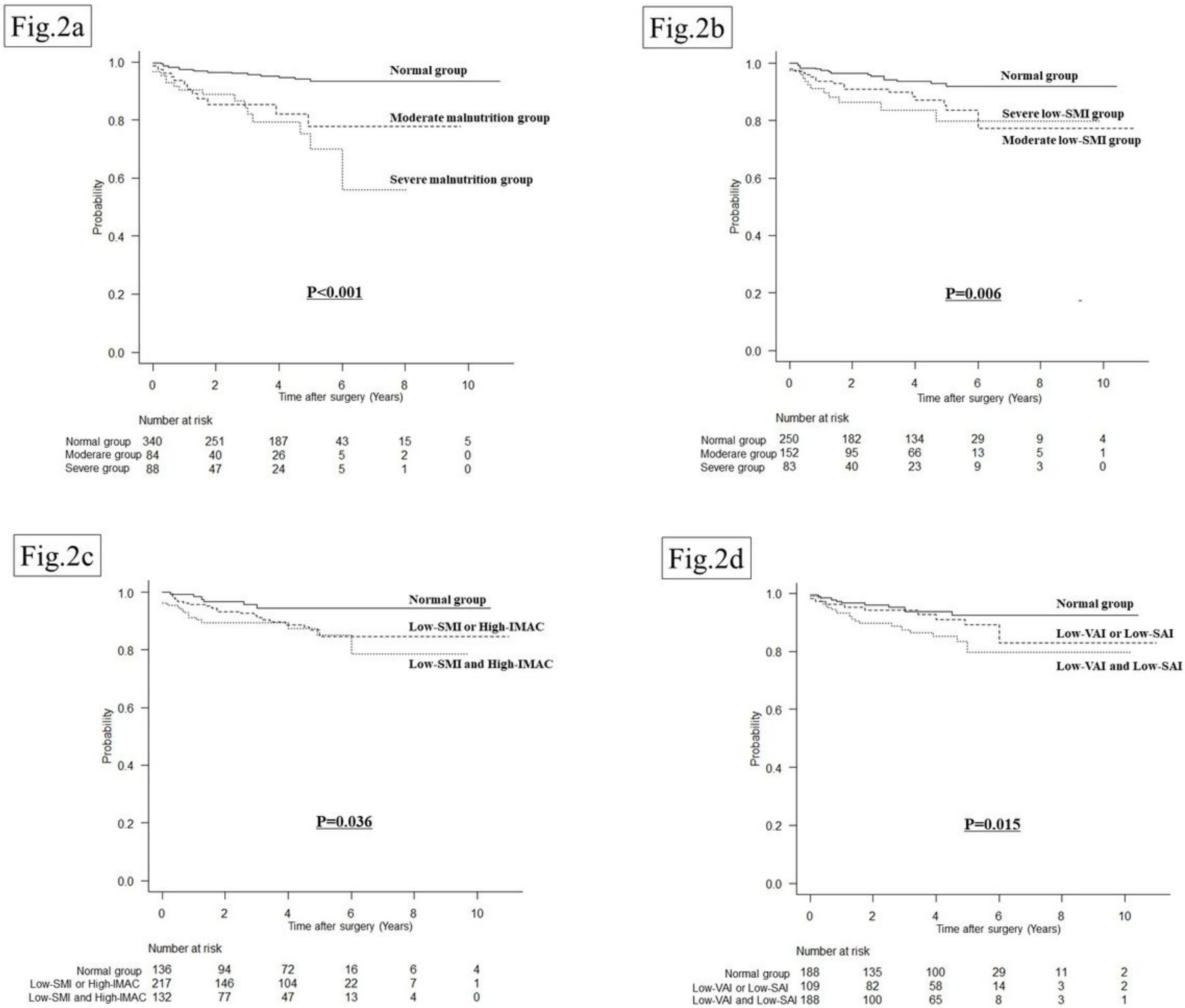

Figure 2

Other-cause survival curves stratified with respect to the following factors:

(a) severity of malnutrition defined by GLIM criteria (P < 0.001),

(b) low-SMI severity (P = 0.006),

(c) low SMI and/or high IMAC (P = 0.036),

(d) low VAI and/or low SAI ($P = 0.015$).