

Cachexia research in Japan: facts and numbers on prevalence, incidence and clinical impact

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Abstract

Even though most clinical data on cachexia have been reported from Western countries, cachexia may be a growing problem in Asia as well, as the population in this area of the world is considerably larger. Considering the current definitions of obesity and sarcopenia in Japan, which are different from the ones in Western countries, the lack of a distinct cachexia definition in Japan is striking. Only one epidemiological study has reported the prevalence of cachexia using weight loss as part of the definition in patients with stage III or IV non-small cell lung cancer. Although the reported prevalence of 45.6% is within the range of that in Western countries (28–57% in advanced cancer), we cannot compare the prevalence of cachexia in other types of cancer, heart failure, chronic obstructive pulmonary disease (COPD), and kidney disease (CKD) between Japan and Western countries. In patients with heart failure, one third of Japanese patients has a body mass index $<20.3 \text{ kg/m}^2$ whereas the prevalence of underweight is 13.6% in reports from Western countries. These results may suggest that there are more cachectic heart failure patients in Japan, or that using the same definition like Western countries leads to gross overestimation of the prevalence of cachexia in Japan. The rate of underweight patients in COPD has been reported as 31–41% in COPD and seems to be high in comparison to the prevalence of cachexia in Western countries (27–35%). The reported lowest quartile value of BMI (19.6 kg/m^2) in CKD may match with the prevalence of cachexia in Western countries (30–60%). The number of clinical trials targeting cachexia is very limited in Japan so far.

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Cachexia is a complex metabolic syndrome associated with underlying illness, characterized by loss of muscle with or without loss of fat mass, and clinically diagnosed by the criteria including existence of underlying chronic disease, significant weight loss, and several evidences of abnormal metabolism.¹ Because of the increasing prevalence of chronic diseases associated with the development of cachexia in advancing age, there is a large number of cachexia-related hospitalizations with increasing costs in Western countries.² Although most clinical data on cachexia have been reported from Western countries, cachexia may be a growing problem because of the larger population in Asia as well.³

As the definition of cachexia includes body weight, we have to pay attention to the fact that the body size in Asian people is different from that in Western countries because of difference in diet, lifestyle, and metabolism.⁴ For example, the cutoff value of the body mass index (BMI) for the

definition of obesity is smaller in Japan than in Western countries ($\geq 25 \text{ kg/m}^2$ in Japan⁵ and $\geq 30 \text{ kg/m}^2$ in Western countries). Hence, there is still some possibility that not only the prevalence but also the ideal therapeutic strategies are different between in Asian people and Caucasians. Research results in Japan as an Asian aged country could become more important both for Asia and western countries.

The present state of cachexia in Japan

Although the researchers in Asia have proposed an Asian definition for sarcopenia, which includes different cutoff values of muscle mass, muscle strength, and physical performance than that for Western countries,^{6,7} there has been no distinct Asian definition for cachexia so far. A simple quotation from the global definition of cachexia⁸ has been included in the

Clinical Guidelines for Infusion Therapy in Advanced Cancer Patients 2013 edited by the Japanese Society for Palliative Medicine, which is the only one cachexia definition with a cutoff for weight loss in Japan.⁹ No other definition of cachexia is shown in guidelines for chronic diseases such as heart failure, chronic obstructive pulmonary disease (COPD), or chronic kidney disease (CKD). Regarding heart failure, unintentional weight loss is alerted as cachexia in Guidelines for Treatment of Acute Heart Failure.¹⁰ For COPD patients, nutritional evaluation including weight assessment are recommended in a section of 'Nutrition management' in the guidelines for the diagnosis and treatment of COPD (3rd edition) without referring to cachexia itself.¹¹ In CKD guidelines, continual diet therapy is recommended without referring to cachexia itself.¹² Lack of distinct cachexia definitions in Japan does not necessarily mean that researchers have accepted the global definition but may rather suggest that many researchers have not paid much attention to cachexia. In fact, there seems to be only one epidemiological research study reporting the prevalence of cachexia using weight loss as a part of the definition. Kimura *et al.* retrospectively reviewed the clinical data of consecutive patients with stage III or IV

non-small cell lung cancer who had received their first-line chemotherapy, after having excluded those who were candidates for curative radiotherapy or who had received palliative radiotherapy.¹³ Cachexia, defined as a body weight loss >5% over the past 6 month or >2% in patients with a BMI <20 kg/m², was observed in 45.6% of the overall cohort, and its presence was associated with a poor prognosis. Although this number is within the range of Western countries (the prevalence ranging from 28 to 57% in advanced cancer¹⁴ and 50–80% in several types of cancer¹⁵), we cannot compare the prevalence of cachexia in other types of cancer, heart failure, COPD, and CKD between Japan and Western countries. Hence, here we listed epidemiologic researches 'suggesting' the prevalence of cachexia, which includes BMI data in chronic diseases (Table 1). In recent years, a significant amount of data has been updated. However, many of these reports^{16–21} had criteria including only BMI cut-off of 18.5 kg/m², which is related to the World Health Organization definition of 'malnutrition'.²² Table 1 includes the data with tertile or quantile value of BMI, if the value is close to 20 kg/m², which is one of the criteria in universal cachexia definition.¹ The lack of data with regards to weight loss in most of

Table 1 Epidemiologic researches suggesting the prevalence of cachexia

Disease	Inclusion criteria	Exclusion criteria	Reference	Definition used	N	Prevalence (%)
Cancer	Advanced NSCLC planned to CT	Patients planned to radiotherapy	Kimura <i>et al.</i> 2015 ¹³	Cachexia	Weight loss >5% over 6 month or >2% in patients with a BMI <20 kg/m ²	134 46
	Head and neck cancer	None	Takenaka <i>et al.</i> 2014 ¹⁶	Underweight	BMI <18.5 kg/m ²	726 18
	Breast cancer planned to CT and surgery	Distant metastasis	Iwase <i>et al.</i> 2014 ¹⁷	Underweight	BMI <18.5 kg/m ²	248 7
	Stomach cancer	None	Minami <i>et al.</i> 2015 ¹⁸	Underweight	BMI <18.5 kg/m ²	1033 8
Chronic HF	Stable HF	None	Nochioka <i>et al.</i> 2010 ¹⁹	Underweight	BMI <18.5 kg/m ²	972 9
	Hospitalized HF	Acute CVD, dialysis, cancer	Takiguchi <i>et al.</i> 2014 ²⁰	Underweight	BMI <18.5 kg/m ²	648 13
	Hospitalized HF	None	Hamaguchi <i>et al.</i> 2010 ²³	Lower tertile in BMI	BMI <20.3 kg/m ²	2488 (33)
	Hospitalized HF	AMI, dialysis, cardiac surgery	Komukai <i>et al.</i> 2012 ⁴²	Lowest quartile in BMI	BMI ≤21.4 kg/m ²	219 (25)
CKD	Hemodialysis	Acute CVD, active infection, cancer	Takahashi <i>et al.</i> 2012 ²⁵	Lowest quartile in BMI	BMI <19.6 kg/m ²	1228 (25)
COPD	Stable COPD	Tuberculosis, cancer	Higashimoto <i>et al.</i> 2011 ²⁶	Low BMI	BMI <20 kg/m ²	69 41
	Hospitalized COPD (>65 y)	None	Yamauchi <i>et al.</i> 2014 ²¹	Underweight	BMI <18.5 kg/m ²	263 940 31

BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CT, Chemotherapy; CVD, cardiovascular diseases; HF, heart failure; NSCLC, non-small cell lung cancer.

the listed reports may be because of the fact that such data cannot be assembled from many databases in retrospect, if the researchers did not record the history of weight loss at the beginning of the studies. According to the epidemiologic data with BMI, one-thirds of Japanese heart failure patients had a BMI $<20.3 \text{ kg/m}^2$ ²³ whereas the prevalence of underweight (BMI $<20.7 \text{ kg/m}^2$) was 13.6% in reports from Western countries.²⁴ These data may suggest that there are more cachectic heart failure patients in Japan than in Western countries, or that the use of the same definition as in Western countries can overestimate the prevalence of cachexia in Japan. Although direct comparisons between Japan and Western countries cannot be performed either in CKD and COPD, the reported lowest quartile value of BMI (19.6 kg/m^2) in CKD²⁵ may match the prevalence of Western countries (30–60%¹⁴). In COPD, the rate of low BMI ($<20 \text{ kg/m}^2$) and underweight (BMI $<18.5 \text{ kg/m}^2$) patients were 41%²⁶ and 31%,²¹ which seem to be high in comparison with the prevalence of cachexia in Western countries (27–35%).¹⁴

Recent cachexia research in Japan

As expected by the lack of epidemiologic data in cachexia, most of observational/interventional studies in Japan have been based on various definitions for cachexia. Table 2 shows observational/interventional parallel-group comparison studies using some clear definitions for cachexia. There are wide difference among studies in the definition of cachexia, although some of them have taken weight loss into account as part of the definition.^{27–33} Four interventional studies using ghrelin and octanoic acid-rich formula have been reported in the field of COPD, including two studies with weight loss $>7.5\%$ over 6 months^{32,33} and 2 studies with BMI $<21 \text{ kg/m}^2$ ^{23,35} as the definition of cachexia. On the other hand, there is no published interventional research targeting cachexia in cancer, heart failure, and CKD. Most of the studies in cancer and heart failure focused on blood levels of hormones or cytokines in those with and without cachexia, but used definitions for cachexia that are completely

Table 2 Observational and interventional studies for cachexia and definitions

Disease	Classification	Reference	Definition of cachexia	Study endpoints	Type of study	N
Cancer	Colorectal and gastric cancer	Shibata <i>et al.</i> 2002 ²⁷	Recurrence or metastasis and $>5\%$ weight loss over 3 months or alb $<3.0 \text{ g/dL}$	The production of cytokines by peripheral blood mononuclear cells	Observational	61
	Lung cancer	Shimizu <i>et al.</i> 2003 ²⁸	Weight loss $>5\%$ over 3 month	Plasma ghrelin levels	Observational	43
	Gastric cancer	Takahashi <i>et al.</i> 2009 ³⁶	Stage IV, subjective symptoms	Plasma ghrelin and leptin levels	Observational	16
	Any cancers	Naito <i>et al.</i> 2012 ³⁷	GPS as a continuous scale	Oxycodone metabolism	Observational	47
	Pancreatic cancer	Fujiwara <i>et al.</i> 2014 ²⁹	Performance Status >0 , anorexia, and weight loss $>10\%$ over 6 months	Serum metabolite levels	Observational	21
	Any cancers	Suno <i>et al.</i> 2015 ³⁰	Weight loss $>5\%$ over 6 month or $>2\%$ in patients with a BMI $<20 \text{ kg/m}^2$ or with sarcopenia	Dose-adjusted plasma fentanyl concentrations	Observational	21
Chronic HF	Stable HF	Nagaya <i>et al.</i> 2001 ³¹	Weight loss $>7.5\%$ over 6 month	Plasma levels of ghrelin and other cytokines	Observational	74
COPD	COPD	Ashitani <i>et al.</i> 2009 ³²	Weight loss $>7.5\%$ over 6 month or BMI $<21 \text{ kg/m}^2$	The effect of an octanoic acid-rich formula on plasma acyl-ghrelin levels	Interventional	23
	COPD	Nagaya <i>et al.</i> 2005 ³³	Weight loss $>7.5\%$ over 6 month	The effects of ghrelin on body composition, muscle strength, and functional capacity	Interventional	7
	COPD	Miki <i>et al.</i> 2012 ³⁴	BMI $<21 \text{ kg/m}^2$	The efficacy and safety of adding ghrelin to pulmonary rehabilitation	Interventional	33
	COPD	Matsumoto <i>et al.</i> 2015 ³⁵	BMI $<21 \text{ kg/m}^2$	The optimal dose of ghrelin	Interventional	44

BMI, body mass index; COPD, chronic obstructive pulmonary diseases; GPS, the glasgow Prognostic Score; calculated using serum albumin and C reacting protein, HF; heart failure.

different from each other. Two of them did not include body weight, but only included cancer stage³⁶ or blood markers³⁷ as definitions of cachexia. The other studies in cancer had an endpoint of weight loss and inflammatory responses^{38,39} without any definition of cachexia. The reasons for such a wide variety of inclusion criteria are not clear, but it could be speculated that the researchers intended to simplify the enrollment of patients.⁴⁰ Although the number of clinical trials targeting cachexia is very limited in Japan so far, researchers may have a potential to produce more evidence in this field, having fruitful results as their background especially in the field of basic research.⁴¹ Further studies targeting cachexia patients defined by universal criteria are desirable when we consider to apply the results for Western countries.

Conclusions

In recent years, many epidemiological data have been updated reporting the distribution of BMI in chronic diseases in Japan, however, most of them have not referred to the definition of cachexia. The clinical course and background of cachectic patients in Japan may be different from that of

patients in Western countries. There have been several observational studies comparing patients with and without cachexia, but the definitions of cachexia used have widely varied among studies. Interventional clinical trials for cachectic patients are still lacking especially in cancer, heart failure, and CKD. Further studies are needed to assess the epidemiologic/pathological background, as well as the effect of therapeutic approach, in cachexia.

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Conflicts of interest

None declared.

References

- Evans WJ, Morley JE, Argiles J, Bales C, Baracos V, Guttridge D, *et al.* Cachexia: a new definition. *Clin Nutr* 2008;**27**:793–799.
- Arthur ST, Noone JM, Van Doren BA, Roy D, Blanchette CM. One-year prevalence, comorbidities and cost of cachexia-related inpatient admissions in the USA. *Drugs Context* 2014;**3**:212265.
- von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* 2010;**1**:1–5.
- Yatsuya H, Li Y, Hilawe EH, Ota A, Wang C, Chiang C, *et al.* Global trend in overweight and obesity and its association with cardiovascular disease incidence. *Circ J* 2014;**78**:2807–2818.
- The Examination Committee of Criteria for ‘Obesity Disease’ in Japan, Japan Society for the Study of Obesity. New criteria for ‘obesity disease’ in Japan. *Circ J* 2002;**66**:987–992.
- Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, *et al.* Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2014;**15**:95–101.
- Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology—update 2014. *J Cachexia Sarcopenia Muscle* 2014;**5**:253–259.
- Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, *et al.* Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011;**12**:489–495.
- Japanese Society for Palliative Medicine. Clinical Guidelines for Infusion Therapy in Advanced Cancer Patients. Available from: <http://www.jspm.ne.jp/guidelines/glhyd/2013/index.php?isbn=9784307101592>. 2013 (cited 2016 Feb.)
- JCS Joint Working Group. Guidelines for treatment of acute heart failure (JCS 2011). *Circ J* 2013;**77**:2157–2201.
- Committee for the Third Edition of the COPD Guidelines of The Japanese Respiratory Society. Guidelines for the Diagnosis and Treatment of COPD 3rd edition edited by the Japanese Respiratory Society. 2010 Available from: <http://www.jrs.or.jp/uploads/uploads/files/photos/765.pdf>. (cited 2016 Feb.)
- Evidence-based practice guideline for the treatment of CKD. *Clin Exp Nephrol* 2009;**13**:537–566.
- Kimura M, Naito T, Kenmotsu H, Taira T, Wakuda K, Oyakawa T, *et al.* Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. *Support Care Cancer* 2015;**23**:1699–1708.
- Farkas J, von Haehling S, Kalantar-Zadeh K, Morley JE, Anker SD, Lainscak M. Cachexia as a major public health problem: frequent, costly, and deadly. *J Cachexia Sarcopenia Muscle* 2013;**4**:173–178.
- von Haehling S, Anker SD. Prevalence, incidence and clinical impact of cachexia: facts and numbers—update 2014. *J Cachexia Sarcopenia Muscle* 2014;**5**:261–263.
- Takenaka Y, Yamamoto M, Nakahara S, Yamamoto Y, Yasui T, Hanamoto A, *et al.* Factors associated with malnutrition in patients with head and neck cancer. *Acta Otolaryngol* 2014;**134**:1079–1085.
- Iwase T, Nakamura R, Yamamoto N, Yoshi A, Itami M, Miyazaki M. The effect of molecular subtype and body mass index on neo-adjuvant chemotherapy in breast cancer patients. *Breast (Edinburgh, Scotland)* 2014;**23**:264–272.
- Minami Y, Kawai M, Fujiya T, Suzuki M, Noguchi T, Yamanami H, *et al.* Family history, body mass index and survival in Japanese patients with stomach cancer: a prospective study. *Int J Cancer* 2015;**136**:411–424.
- Nochioka K, Shiba N, Kohno H, Miura M, Shimokawa H. Both high and low body mass indexes are prognostic risks in Japanese patients with chronic heart failure: implications from the CHART study. *J Card Fail* 2010;**16**:880–887.
- Tagiguchi M, Yoshihisa A, Miura S, Shimizu T, Nakamura Y, Yamauchi H, *et al.* Impact of body mass index on mortality in heart failure patients. *Eur J Clin Invest* 2014;**44**:1197–1205.
- Yamauchi Y, Hasegawa W, Yasunaga H, Sunohara M, Jo T, Takami K, *et al.* Paradoxical association between body mass index and in-hospital mortality in elderly patients with chronic obstructive pulmonary disease in

- Japan. *Int J Chron Obstruct Pulmon Dis* 2014;**9**:1337–1346.
22. [No authors listed] Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organization technical report series. 1995;**854**:1–452.
23. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Goto D, Yokota T, Goto K, *et al*. Body mass index is an independent predictor of long-term outcomes in patients hospitalized with heart failure in Japan. *Circ J* 2010;**74**:2605–2611.
24. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;**38**:789–795.
25. Takahashi R, Ito Y, Takahashi H, Ishii H, Kasuga H, Mizuno M, *et al*. Combined values of serum albumin, C-reactive protein and body mass index at dialysis initiation accurately predicts long-term mortality. *Am J Nephrol* 2012;**36**:136–143.
26. Higashimoto Y, Yamagata T, Honda N, Satoh R, Sano H, Iwanaga T, *et al*. Clinical and inflammatory factors associated with body mass index in elderly patients with chronic obstructive pulmonary disease. *Geriatr Gerontol Int* 2011;**11**:32–38.
27. Shibata M, Nezu T, Kanou H, Abe H, Takekawa M, Fukuzawa M. Decreased production of interleukin-12 and type 2 immune responses are marked in cachectic patients with colorectal and gastric cancer. *J Clin Gastroenterol* 2002;**34**:416–420.
28. Shimizu Y, Nagaya N, Isobe T, Imazu M, Okumura H, Hosoda H, *et al*. Increased plasma ghrelin level in lung cancer cachexia. *Clin Cancer Res* 2003;**9**:774–778.
29. Fujiwara Y, Kobayashi T, Chayahara N, Imamura Y, Toyoda M, Kiyota N, *et al*. Metabolomics evaluation of serum markers for cachexia and their intra-day variation in patients with advanced pancreatic cancer. *PLoS One* 2014;**9**: e113259.
30. Suno M, Endo Y, Nishie H, Kajizono M, Sendo T, Matsuoka J. Refractory cachexia is associated with increased plasma concentrations of fentanyl in cancer patients. *Therapeutics and Clinical Risk Management* 2015;**11**:751–757.
31. Nagaya N, Uematsu M, Kojima M, Date Y, Nakazato M, Okumura H, *et al*. Elevated circulating level of ghrelin in cachexia associated with chronic heart failure: relationships between ghrelin and anabolic/catabolic factors. *Circulation* 2001;**104**:2034–2038.
32. Ashitani J, Matsumoto N, Nakazato M. Effect of octanoic acid-rich formula on plasma ghrelin levels in cachectic patients with chronic respiratory disease. *Nutr J* 2009;**8**:25.
33. Nagaya N, Itoh T, Murakami S, Oya H, Uematsu M, Miyatake K, *et al*. Treatment of cachexia with ghrelin in patients with COPD. *Chest* 2005 Sep;**128**:1187–1193.
34. Miki K, Maekura R, Nagaya N, Nakazato M, Kimura H, Murakami S, *et al*. Ghrelin treatment of cachectic patients with chronic obstructive pulmonary disease: a multicenter, randomized, double-blind, placebo-controlled trial. *PLoS One* 2012;**7**:e35708.
35. Matsumoto N, Miki K, Tsubouchi H, Sakamoto A, Arimura Y, Yanagi S, *et al*. Ghrelin administration for chronic respiratory failure: a randomized dose-comparison trial. *Lung* 2015;**193**:239–247.
36. Takahashi M, Terashima M, Takagane A, Oyama K, Fujiwara H, Wakabayashi G. Ghrelin and leptin levels in cachectic patients with cancer of the digestive organs. *Int J Clin Oncol* 2009;**14**:315–320.
37. Naito T, Tashiro M, Yamamoto K, Ohnishi K, Kagawa Y, Kawakami J. Impact of cachexia on pharmacokinetic disposition of and clinical responses to oxycodone in cancer patients. *Eur J Clin Pharmacol* 2012;**68**:1411–1418.
38. Takata A, Takiguchi S, Miyazaki Y, Miyata H, Takahashi T, Kurokawa Y, *et al*. Randomized phase II study of the anti-inflammatory effect of ghrelin during the postoperative period of esophagectomy. *Ann Surg* 2015;**262**:230–236.
39. Sakamoto M, Mikasa K, Majima T, Hamada K, Konishi M, Maeda K, *et al*. Anti-cachectic effect of clarithromycin for patients with unresectable non-small cell lung cancer. *Chemotherapy* 2001;**47**:444–451.
40. Fearon K, Argiles JM, Baracos VE, Bernabei R, Coats A, Crawford J, *et al*. Request for regulatory guidance for cancer cachexia intervention trials. *J Cachexia Sarcopenia Muscle* 2015;**6**:272–274.
41. Ebner N, Steinbeck L, Doehner W, Anker SD, von Haehling S. Highlights from the 7th Cachexia Conference: muscle wasting pathophysiological detection and novel treatment strategies. *J Cachexia Sarcopenia Muscle* 2014 Mar;**5**:27–34.
42. Komukai K, Minai K, Arase S, Ogawa T, Nakane T, Nagoshi T, *et al*. Impact of body mass index on clinical outcome in patients hospitalized with congestive heart failure. *Circ J* 2012;**76**:145–151.
43. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015. *J Cachexia Sarcopenia Muscle* 2015;**6**: 315–316.