Editorial

Sarcopenia, obesity and postoperative outcomes after hepatectomy for hepatocellular carcinoma

Michele Molinari

Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Correspondence to: Michele Molinari. Department of Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA. Email: molinarim@upmc.edu.

Provenance and Peer Review: This article was commissioned by the Editorial Office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Comment on: Kobayashi A, Kaido T, Hamaguchi Y, *et al*. Impact of Sarcopenic Obesity on Outcomes in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma. Ann Surg 2019;269:924-31.

Submitted Sep 11, 2019. Accepted for publication Sep 18, 2019.

doi: 10.21037/hbsn.2019.09.12

View this article at: http://dx.doi.org/10.21037/hbsn.2019.09.12

Over the last few decades, we have learned that the composition of our body is directly related to our health. The second and equally important lesson is that when we define a healthy body, we have to go beyond the ratio between the weight and the height of a person. The third lesson is that even though a “normal” balance between body fat and muscle is associated with good health and longevity, we still do not know what a “normal body composition” is.

Human bodies can be classified in three main phenotypes based on the work of William Sheldon (1), a constitutional psychologist who worked at Harvard University in the 1940s. The three phenotypes are: ectomorphic, mesomorphic and endomorphic. While we have certain tendency toward one group or the other, the level or physical activity, diet, age, gender or the presence of diseases have a profound impact that can make us migrate from one phenotype to another over time (2).

Despite the challenge represented by the lack of a simple and universal measure of body composition, the efforts to better understand its impact has grown exponentially. This was probably triggered by the fact that in the early 1980s, the prevalence of obesity started to reach epidemic levels in most of the high-income countries. This was paralleled by a significant decline of physical activity (3).

Over the last 40 years, we have learned that obesity causes many conditions including diabetes, cardiovascular diseases, osteoarthritis and some types of malignancies (4). On the other hand, the impact of muscles mass on our health (5) has been unrecognized for a longer period. Only in more recent years we have appreciated that there is a tight relationship between adiposity and free-fat body mass.

Besides insufficient physical activity, sarcopenia can be induced by advanced age, inadequate dietary intake, inflammatory and endocrine diseases, organ failure and malignancies. And since obesity is associated with an increased level of pro-inflammatory cytokines and decreased motility, it is not surprising that 15–30% of obese patients are also sarcopenic.

The first studies on how to measure muscle mass in the human body were performed by Garn in the early 1960s (6). However, in the medical literature, the very first publications on the relationship between sarcopenia and longevity appeared only in the early 1990s (7-9). It took about 30 years before we realized that low muscle mass has a negative effect on our health. It took another 20 years to apply that concept to patients undergoing liver resections.

In 2011, Peng *et al.* (10) were the first group to report that in comparison to their counterparts, sarcopenic patients with colorectal hepatic metastases had an increased risk of postoperative morbidity and longer hospital stay but similar overall and disease-free survival. Their observation was challenged one year later by van Vledder *et al.* (11) who found that survival rates after hepatic resection were inferior in patients with sarcopenia and colorectal metastases.

Over the following years, there has been an increasing number of studies that analyzed the role of sarcopenia in patients undergoing liver resections for both primary and secondary malignancies. In 2013, Harimoto *et al.* (12) described that 40% of patients undergoing hepatic resection for hepatocellular carcinoma (HCC) had sarcopenia. More importantly, they reported that their disease free (13% *vs.* 33%) and overall 5-year survivals (71% *vs.* 83%) were significantly lower than patients without sarcopenia. These results were confirmed two years later by Voron *et al.* (13) who reported their experience with 198 patients who had hepatic resection for HCC in France and by Levolger *et al.* (14) who studied 90 patients operated in the Netherlands.

In 2015, another important observation was made by Hamaguchi *et al.* (15) from the university of Kyoto. In their study, they found that patients with intramuscular adipose tissue undergoing hepatic resections for HCC, the risk of postoperative mortality was higher, and their overall and disease-free survival rates were inferior than patients with normal muscle composition. This study was important as it revealed that adipose and muscular tissues are not two separate and independent entities. Therefore, our understanding of body composition needed to be reframed.

This process occurred over the following 2 years in both surgical oncology and in the field of transplantation. Hepatobiliary, pancreatic, and liver transplant specialists started studying the outcomes of patients undergoing surgery with a better understanding that their body composition played a significant role in the short and long-term outcomes. In addition, they became more knowledgeable in stratifying patients using more refined methods to categorize body compositions.

The first landmark study that assessed the effects of the combination of sarcopenia and obesity (SO) in resected patients for HCC in Japan was published in the Annals of Surgery in 2017 by Kobayashi *et al.* (16). In the paper entitled "Impact of Sarcopenia Obesity on Outcomes in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma", the authors addressed a very important issue faced by many healthcare providers treating patients with primary hepatic malignancies. The authors performed a retrospective analysis of 465 patients who underwent a primary hepatectomy for HCC at Kyoto University Hospital between April 2005 and March 2015. For each participant, the authors measured the skeletal muscle and visceral adipose tissue using the latest preoperative enhanced abdominal CT scan.

Using validated methodologies, the areas of the psoas, paraspinal and abdominal wall muscles were calculated at the level of the third lumbar vertebrae (L3) as described by many other groups in the past. Similarly, the adipose tissue was calculated at the level of the umbilicus. The quantity of skeletal muscle was transformed in skeletal muscle index (SMI) by normalizing the areas of the skeletal muscle (cm^2) by the height of the patient (m^2). Since SMI differs between males and females, normal cutoff values for SMI were defined as 40.31 cm^2/m^2 for males and 30.88 cm^2/m^2 for females. On the other hand, obesity was defined as the presence of an area of visceral adipose tissue >100 cm^2 in both sexes.

The innovative part of this study was that the authors stratified the study population in four groups. The first group represented patients who had normal muscle mass and normal weight [non-sarcopenia and non-obese (NN) =184]. The second group was made by patients who had normal muscle mass but were obese [non-sarcopenia and obesity (NO) =219]. The third group represented patients with sarcopenia but who were non-obese [sarcopenia and non-obesity (SN) =31] and the last group was represented by patients who had both SO [SO =31].

Compared to the other groups, SO patients were more frequently males, older and with Child-Pugh class B and less frequently affected by hepatitis B or C. On the other hand, oncological parameters such as tumor size, the number of lesions, presence of vascular invasion and cellular differentiation were similar among the four groups.

The authors reported several important findings. First, even if the extent of the surgical procedures, blood losses and the overall postoperative morbidity were similar among groups, the rate of major complications was significantly higher for SN and SO patients in comparison to NO patients (16.9% *vs.* 38.7% and 16.9% *vs.* 32.3% respectively: P=0.016).

Second, 1-, 3- and 5-year overall survivals were lower for patients with SN and SO in comparison to NN patients (91%, 78%, 61% for NN, versus 77%, 62%, 38% for SN, P=0.170, versus 83%, 45% and 45% for SO respectively, P=0.02). When compared to NN, patients with SO had a significantly lower recurrent-free survival at 1 and 3 years (64.4% *vs.* 33.8%) and (37.8% *vs.* 19.3%) respectively (P=0.03). At multivariable analysis, after adjusting for various confounders, SO remained an independent risk factor for inferior overall survival (HR 2.504; 95%CI, 1.336–4.499) and disease-free survival (HR 2.031; 95%CI, 1.233–3.222).

Besides the retrospective design, the relatively small number of patients who had both SO (n=31), the homogenous population, the lack of details about the attrition rate and how missing data were handled, this study has many strengths and several important points, can be drawn. The first one is that despite the fact that patients underwent surgery in one of the best centers in the world, the presence of sarcopenia was an independent factor associated with increased morbidity and lower survival. Second, isolated obesity was not a negative factor for postoperative morbidity and mortality after hepatic resection. Third, and the most important one, the combined presence of obesity and sarcopenia was a risk factor for inferior survival with a hazard ratio of 2.5 (95% CI, 1.3–4.4), a value that was even higher than tumors in advanced stages (hazard ratio for TNM III–IV =2.2; 95% CI, 1.3–3.9).

I suspect that this paper will remain the reference study for the impact of body composition on the outcomes of patients undergoing hepatic resection for HCC for a long time. Since obesity is a very prevalent condition in many societies, and sarcopenia is very common in elderly patients and individuals with chronic liver disease and malignancies, Kobayashi and colleagues (16) provided us a great piece of evidence that tumor stage is not the only and most important predicting factor for the long-term outcomes of patients who undergo hepatic resection for HCC.

Since HCC is one of the most common solid tumors of the gastrointestinal tract in the world, the ageing of societies in many developed countries where overweight and obese individuals are the majority of the population, we conclude that this study is a landmark paper that open the door for future research to address the following gaps:

(I) The lack of standardized definitions and methodologies for the measurement of body composition;
(II) The limited role given to preoperative programs that could optimize the body composition of patients at increased risk of poor outcomes after hepatic surgery;
(III) Our partial knowledge on the key molecular pathways associated with obesity and sarcopenia;
(IV) Our inability to modulate biological pathways that could decrease sarcopenia and sarcopenic obesity in patients with HCC or other malignancies treatable by hepatic resection.

In conclusion, we commend Kobayashi and colleagues (16) for their excellent study and for giving us a clearer picture on the impact of body composition on both short and long-term outcomes of patients undergoing hepatic resection for HCC. One of the main messages that emerge from their study is that for meaningful advances in the field where surgery, oncology, nutrition, physical capacity and aging intersect, we should start standardizing definitions and measurements, and we should find strategies to help patients to migrate away from high-risk groups. Probably, one of the most immediate, safest, most inexpensive therapeutic interventions is to convince our patients to exercise. However, I suspect that this task might be the most difficult to tackle.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn.2019.09.12/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sheldon WH. Varieties of delinquent youth. An introduction to constitutional psychology. Harper and Brothers, 1949.
2. Waters DL, Baumgartner RN. Sarcopenia and obesity. Clin Geriatr Med 2011;27:401-21.
3. Meldrum DR, Morris MA, Gambone JC. Obesity pandemic: causes, consequences, and solutions-but do we have the will? Fertil Steril 2017;107:833-9.
4. The American Cancer Society medical and editorial content team. Does Body Weight Affect Cancer Risk?

2015. Available online: https://www.cancer.org/cancer/cancer-causes/diet-physical-activity/body-weight-and-cancer-risk/effects.html
5. Ng SW, Popkin BM. Time use and physical activity: a shift away from movement across the globe. Obes Rev 2012;13:659-80.
6. Garn SM. Radiographic analysis of body composition. In: Brožek J, Henschel A. editors. Techniques for measuring body composition. 1961:36-58.
7. Tayback M, Kumanyika S, Chee E. Body weight as a risk factor in the elderly. Arch Intern Med 1990;150:1065-72.
8. Yao CH, Slattery ML, Jacobs DR Jr, et al. Anthropometric predictors of coronary heart disease and total mortality: findings from the US Railroad Study. Am J Epidemiol 1991;134:1278-89.
9. Wienpahl J, Ragland DR, Sidney S. Body mass index and 15-year mortality in a cohort of black men and women. J Clin Epidemiol 1990;43:949-60.
10. Peng PD, van Vledder MG, Tsai S, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB (Oxford) 2011;13:439-46.
11. van Vledder MG, Levolger S, Ayez N, et al. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg 2012;99:550-7.
12. Harimoto N, Shirabe K, Yamashita YI, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 2013;100:1523-30.
13. Voron T, Tselikas L, Pietrasz D, et al. Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma. Ann Surg 2015;261:1173-83.
14. Levolger S, van Vledder MG, Muslem R, et al. Sarcopenia impairs survival in patients with potentially curable hepatocellular carcinoma. J Surg Oncol 2015;112:208-13.
15. Hamaguchi Y, Kaido T, Okumura S, et al. Preoperative intramuscular adipose tissue content is a novel prognostic predictor after hepatectomy for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci 2015;22:475-85.
16. Kobayashi A, Kaido T, Hamaguchi Y, et al. Impact of Sarcopenic Obesity on Outcomes in Patients Undergoing Hepatectomy for Hepatocellular Carcinoma. Ann Surg 2019;269:924-31.

Cite this article as: Molinari M. Sarcopenia, obesity and postoperative outcomes after hepatectomy for hepatocellular carcinoma. HepatoBiliary Surg Nutr 2020;9(2):198-201. doi: 10.21037/hbsn.2019.09.12

