Sarcopenia in Hepatocellular Carcinoma: Pathogenesis and Management

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Keywords

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Abstract

Background: Sarcopenia is almost constantly observed in patients with cirrhosis and hepatocellular carcinoma (HCC).

Summary: Chronic liver disease represents a unique pathophysiological scenario in which sarcopenia develops and all factors involved in the pathogenesis should be taken into account for an appropriate management of the disease. No properly designed intervention studies on this topic are available and, thus, no effective strategies have been developed for clinical practice. Apart from any targeted intervention, treatment, and optimization of liver disease is crucial.

Key Messages: In patients with cirrhosis and HCC, nutritional support to maintain and restore nutrition status, a targeted use of branched-chain amino acids and a guided physical exercise, should all be an integral part of the multidimensional assessment and tailored interventions.

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Introduction

Hepatocellular Carcinoma

Liver cancer is the fourth most frequent cause of cancer-related death in the world and is associated with high rates of mortality [1]. Hepatocellular carcinoma (HCC) represents the principal form of primary liver cancer, and major risk factors for HCC include cirrhosis caused by chronic infection with the hepatitis C and hepatitis B viruses, heavy alcohol drinking, and above all in recent years, non-alcoholic fatty liver disease that is already the fastest growing cause of HCC in Western countries [2–4]. As most patients with HCC have underlying cirrhosis, a multidisciplinary evaluation including tumour stage, liver function, and performance status, as well as comorbidities, is essential in therapeutic decision-making [5].

Early diagnosis in patients with a well-preserved liver function is crucial to facilitate curative therapy. When patients are not suitable for surgery, transplantation or locoregional treatments, systemic therapy is the choice. The multikinase inhibitor sorafenib has been for long time the only systemic treatment available for advanced HCC. Recently,

various trials have reported a clinical benefit and prolonged survival (more than 2 years) in advanced HCC for the tyrosine kinase inhibitors (TKIs) (lenvatinib, regorafenib, and cabozantinib), for an angiostatic antibody (ramucirumab) and for immune checkpoint inhibitors, alone or in combination (nivolumab, pembrolizumab, atezolizumab in combination with bevacizumab and ipilimumab in combination with nivolumab). Some of these drugs have been approved so far as first or second-line treatment by national agencies [5, 6]. This new scenario has opened opportunities in the choice and sequential application of systemic treatments and has made even more important selection of patients and the shift to systemic treatment lines prior to the onset of critical hepatic dysfunction, when best supportive care becomes the only reasonable option.

From this perspective, the general assessment of patients becomes crucial and a multidisciplinary approach is essential. However, actual staging and prognostic systems do not include parameters assessing the functional and nutritional status notwithstanding these factors have already been associated with outcomes in patients with cancers [7].

In the last decade, research has focused its attention on the role of sarcopenia and frailty in chronic liver disease (CLD) as modifiable (if early identified) factors whose recognition and periodical assessment is critical because of strong association with morbidity, mortality, and quality of life [8–10]. Depending on the population evaluated, the prevalence of sarcopenia and frailty in cirrhotic liver disease is very high and estimated from 40 to 70% and 18–43% [11–14], respectively. Therefore, starting from these assumptions, the aim of this review is to describe the complex pathophysiology and the role of assessment and management of sarcopenia in patients with cirrhosis and HCC.

Sarcopenia in CLD

Sarcopenia is a very common complication observed in patients with cirrhosis [11, 12] and differently from geriatric literature [10], it is mainly diagnosed in the clinical setting using operational definitions based on low muscle mass. Various techniques have been applied to quantify muscle mass in this context and, to date, the most well-validated tools are the psoas and lumbar vertebral body cross-sectional imaging assessments by computed tomography or magnetic resonance imaging [15, 16]. Several studies have shown that total skeletal muscle index estimated at the level of L3 vertebra is the most accurate predictor of whole-body muscle mass [17–20].

Anyhow, while the North American collaboration cut-offs for the diagnosis of sarcopenia are the most widely used criteria (skeletal muscle index $<50 \text{ cm}^2/\text{m}^2$ in males $<39 \text{ cm}^2/\text{m}^2$ in females) [21], studies on the validation of computed tomography\ magnetic resonance imaging in the overall population and on the application of other tools in the cirrhotic patients are still missing and needed (Table 1). Ultrasound evaluation is easy and readily available, but its use for the diagnosis of sarcopenia is still in promising steps. Bioimpedance analysis and dual-energy X-ray absorptiometry are not always available, and accuracy among cirrhotic patients might suffer from the interference of ascites and fluid retention. Handgrip strength has been associated with adverse clinical outcomes in patients with end-stage liver disease [21] but it may not be accurate when normalized to body mass index in cirrhosis due to fluctuating body water content [22, 23].

Most studies on sarcopenia in CLD have been conducted in patients awaiting liver transplantation, where sarcopenia is associated with an increased risk of complications and negative outcomes [24, 25]. Extensive data (even if heterogeneous) support the prognostic role of sarcopenia even in patients with compensated or decompensated CLD outside the transplant setting [26]. Moreover, literature clearly shows that, regardless of liver function, sarcopenia is associated with the risk of complications (hepatic encephalopathy (HE), infection, and delirium.) [24, 27, 28], hospitalization [29], higher healthcare costs [29], and mortality in CLD [12, 30–32], and is correlated with negative outcomes and poor survival in patients with HCC [33]. Nowadays, sarcopenia is one of the several pathogenic mechanisms that have contributed to the worse prognosis and higher mortality of cirrhotic patients with severe COVID-19 infection [34].

On the one hand, it is well known the prognostic negative role of sarcopenia in all patients with various forms of cancer and its association with overall reduced survival [7]. On the other hand, it should be emphasized that in patients with HCC complicating cirrhosis, the pathophysiological substrate of sarcopenia is more complex, outlining a unique pathology setting whose identification and treatment in early stages becomes even more important.

Physiopathology of Sarcopenia in Cirrhosis and Cancer

In liver disease, sarcopenia is a multifactorial process whose mechanisms have not been extensively clarified since few preclinical and clinical studies have been devel-

Table 1. Commonly used methods to assess sarcopenia in cirrhosis

Methods	Pros	Cons and unmet needs
CT scan SMI at the 3rd lumbar vertebrae	Assessment of muscle quality and quantity No interference from ascites Well-validated as a predictor of mortality	Expensive and with radiation exposure No standardized cut-off in overall population and cirrhotic patients
CT psoas muscle thickness adjusted for height and psoas muscle area	Assessment of muscle quality and quantity No interference from ascites	Less-validated as a predictor of mortality Expensive and with radiation exposure No standardized cut-off in overall population and cirrhotic patients
DEXA appendicular and upper limb lean mass-height adjusted	Highly precise measure of lean mass Validated in cirrhotic population Low radiation exposure	Interference of fluid retention No data as a predictor of mortality
BIA	Inexpensive, fast and without radiation exposure	Interference of fluid retention and ascites No data as a predictor of mortality No well validation in cirrhotic patients
Ultrasound (Quadriceps muscle diameter and muscle psoas index)	Inexpensive, fast and without radiation exposure	Inter- and intra-operator variability No data as a predictor of mortality No validation in large cohorts and clinical practice
HGS	Inexpensive, simple and reproducible Assessment of muscle function (not mass)	Affected by hepatic complications (i.e., encephalopathy) No validation in large cohorts and clinical practice

DEXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance; CT, computed tomography; SMI, skeletal muscle index; HGS, handgrip strength.

Fig. 1. Principal physiopathological mechanisms of sarcopenia in patients with liver cirrhosis and HCC.

oped in humans [35]. Malabsorption, hyperammonemia, metabolism alteration, hormonal defects, and overall increased muscle loss are all considered potential contributors to disease development (Fig. 1). In addition, sarcopenia can cause an overestimation of renal function based

on serum creatinine, both because of a concomitant reduced hepatic production of creatinine and of a low rate of creatinine conversion due to skeletal muscle mass loss [36, 37].

Malabsorption and Metabolism Alterations

Inadequate nutrients intake is frequently observed in cirrhotic patients [38], generally due to several causes: altered taste induced by vitamin deficiency and dietetic restrictions [39]; increased abdominal pressure caused by ascites [39]; impaired gastrointestinal motility associated to portal hypertension [40]; altered bile flow in the gut that contributes to fat malabsorption and is associated with bacterial overgrowth and inflammation [41].

Furthermore, cirrhosis is a condition of accelerated starvation and hypermetabolic state that increases the demand for proteins and calories [42]. Within a short period of fasting (10 h in patients of cirrhosis are equivalent to 3 days of starvation in a healthy subject [43]), because of the limited hepatic glycogen stores, there is an excessive consumption of body fats and proteins used for gluconeogenesis [44] with the degradation of skeletal muscle proteins to make gluconeogenic substrates available. Moreover, hepatic gluconeogenesis is enhanced in patients with cancer as HCC, probably to provide the tumour cells with de novo synthesized glucose [45]. The overall increased utilization of amino acids results in reduced levels of plasma branched-chain amino acids (BCAAs) and, as a consequence, in reduced supply of this preferred energy source to the skeletal muscles with further muscle degradation [46–48].

Hormonal Defects and Increase Muscle Loss

Male patients with cirrhosis have low testosterone levels [49]. Testosterone improves protein synthesis and muscle mass activating mammalian target of rapamycin through insulin-like growth factor-1 [50] and is responsible of the downregulation of myostatin whose activation is involved in the pathogenesis of muscle wasting in sarcopenia or cachexia associated with different diseases [51, 52]. Indeed, elevated myostatin levels may have a significant role in increasing muscle loss since this myokine negatively regulates the proliferation and the differentiation of satellite cells [53]. In addition, proteostasis in cirrhosis is unbalanced in favour of proteolysis [54] as a result, among others, of the chronic inflammation with elevated levels of pro-inflammatory cytokines [55].

Hyperammonemia

Hyperammonemia plays a relevant role in cirrhosis as part of the liver-muscle axis contributing to the development of sarcopenia. Ammonia disposal is impaired in cirrhosis due to hepatocyte dysfunction and portosystemic shunting [56]. In this context, muscle plays a relevant compensatory role in removing ammonia by transforming glutamate into glutamine through the presence of the

enzyme glutamine synthase [57], and therefore, sarcopenia hastens the development of HE [58]. Moreover, hyperammonaemia mediates the activation of p65-nuclear factor kappa B that is associated with an increased expression of myostatin [59]. At the same time, it impairs the tricarboxylic acid cycle ultimately entailing a reduction of protein synthesis [35]. Lastly, an altered flux of the essential amino acid L-leucine in the muscle plays another important role in this physiopathological process [60].

Cancer and Sarcopenia

In addition to the mechanisms involved in the development of sarcopenia in CLD, patients with HCC develop a sarcopenia secondary to tumour burden that derives, in a more peculiar way, from the systemic cytokine-mediated inflammation observed in cancer [61]. Muscle loss is further exacerbated by some age-related features (physical inactivity, malnutrition, and hormonal alterations) typically observed in patients with cancer [62]. Sarcopenic patients have a poorer tolerance to cancer treatments and a greater incidence of complications (infection, chemotherapy toxicity, and perioperative problems) is observed [63]. Furthermore, patients with cancer develop a syndrome of cachexia that is another multifactorial disease similar to sarcopenia but characterized not only by muscle loss but also by total body weight loss [64]. There is a considerable overlap in the development of cachexia and sarcopenia and these conditions may coexist. Generally, cancer cachexia is caused by a complex interplay between anorexia, increased protein catabolism, systemic inflammation, and increased resting state energy expenditure with inflammation playing a more relevant role, respect to sarcopenia, in the development of cachexia [65].

HCC Treatment Settings and Sarcopenia

Surgery and Liver Transplant

The role of sarcopenia in the development and prognosis of patients undergoing hepatic resection for HCC has been evaluated in many studies conducted in the last decade. It has been clearly shown that sarcopenia is correlated with impaired liver function and with a worse prognosis after liver surgery respect to overall and recurrence-free survival [66–68]. Moreover, sarcopenia has been correlated with the stage and histological features of tumours (stage, presence of satellite nodules, and dedifferentiation in liver histology) [67, 68], and the risk of recurrence after liver resection was found to be associated

to sarcopenic obesity [69, 70] that is significantly linked with poorer overall survival in all patients with cancer [71]. In addition, sarcopenic patients undergoing hepatic resection have shown a functional smaller liver volume compared to the non-sarcopenic ones and they are at increased risk of complications, longer hospitalization, negative outcomes, and liver failure [72, 73].

These data are even more robust in the transplantation setting where most of the studies on sarcopenia in liver disease have been developed [12, 25, 48]. These studies confirm the correlation between sarcopenia and survival among liver transplantation candidates [12] to such an extent that modification of model for end-stage liver disease (MELD)-score, to include sarcopenia, has been proposed and has shown to perform better than MELD in predicting mortality in cirrhotic patients awaiting transplantation (mainly in patients with low MELD scores) [12]. Finally, sarcopenia was found to be associated with worse post-operative outcomes (complications, hospital stay, and overall survival) even after liver transplantation [74].

Local and Locoregional Treatments

Local and locoregional treatments are the recommended strategies for a large proportion of subjects with HCC (BCLC stage 0-A-B) [75]. Few studies have focused their attention on the prognostic role of sarcopenia in these settings [76–81]. Overall, most studies [78, 79] showed that pre-treatment low muscle mass is an independent risk factor for reduced survival. When evaluated, the reduction of muscle mass over time after locoregional treatments was always associated with poorer outcomes [78, 79].

In any case, many methodological drawbacks currently hamper firm conclusions on this topic and should be adequately taken into account when facing with often heterogeneous results. Firstly, many different districts and measures of sarcopenia were applied, and in 2 studies, patients with both primary and secondary liver tumours were included [77, 80]. This clearly makes available data poorly comparable, and significantly limits the consistency of reported results. Secondly, the only studies evaluating the impact of sarcopenia on treatment response and post-procedural morbidity found inconsistent associations [77, 80], suggesting the prognostic impact of sarcopenia on locoregional procedure to depend more deeply upon its role over the general clinical conditions of cirrhotic patients with HCC, rather than on its role on the efficacy of the procedure. Finally, most of the data are derived from retrospective studies including a relatively small number of patients.

Systemic Treatment

A comprehensive assessment is one of the major determinants of choice in cancer patient candidates to systemic treatment. In addition to the clinical performance status scales (such as Karnofsky and ECOG performance scale), sarcopenia represents an objective parameter to better select and follow patients when systemic treatment is the chosen strategy. Several retrospective studies demonstrated a correlation between sarcopenia and worse outcomes in cancer patients treated with antineoplastic drugs. A recent meta-analysis [82] correlates sarcopenia with mortality analysing different cancers during systemic treatment. In a cohort of patients affected by primary liver cancers, mortality was more than doubled and pre-treatment sarcopenia reduced the efficacy of anticancer therapy in terms of response rate inducing lower drug tolerability and higher toxicity [83, 84]. Moreover, systemic treatments exacerbate muscle loss through the intrinsic mechanisms of action of some drugs and through various side effects promoting muscle mass depletion [85].

Sarcopenia and TKIs

In an interesting systematic review and meta-analysis assessing the prognostic role of muscle mass loss in patients treated with TKIs in different cancer types, a strong association was reported between sarcopenia and poor overall survival, as well as dose-limiting toxicities, in patient affected by HCC and treated with sorafenib. In literature, the majority of retrospective studies aiming to analyse the effect of sarcopenia in HCC patients under systemic treatment concerns patients undergoing sorafenib treatment, as a result of a longer clinical availability.

With sorafenib administration, Mir et al. [86] showed a higher prevalence of dose-limiting toxicity in sarcopenic patients that, interestingly, were more frequently treated with an initial dose of 200 mg b.i.d. as a clinical choice of the physician. In other 2 retrospective studies [87, 88], sarcopenia was reported as an independent prognostic factor for overall survival and for treatment interruption. Moreover, sarcopenia was shown to be a good predictor of drug toxicity in patients treated with lenvatinib and was correlated with lenvatinib tolerability [89, 90].

Lastly, as mentioned above, there is also evidence that systemic drugs could favour sarcopenia through direct mechanisms since, for example, TKI downstream signaling includes alterations of phosphatidylinositol-3-kinase/AKT-mammalian target of rapamycin pathway, that is physiologically implied in muscle protein synthesis [91] whose dysregulation induced by drugs could favour further muscle loss [92].

Fig. 2. Proposed strategy to treat sarcopenia in patients with liver cirrhosis and HCC.

Sarcopenia and Immunotherapy

Immunotherapy is becoming the frontline standard of care in patients affected by advanced HCC. The pathogenic mechanism of sarcopenia in this setting may be explained by the interplay between skeletal muscle and the immune system. The same cytokines implicated in sarcopenia, such as TGF- β and IL-6, have also been cited as mediators of T-cell exhaustion. Therefore, the decreased muscle mass may have a direct link to immune dysregulation, resistance to immune checkpoint inhibitors, and poorer outcomes in patients with cancer treated with these agents [93]. Several studies have assessed the relationship between sarcopenia and immunotherapy in cancer, especially in breast and lung cancer, and have shown a lower objective disease control and a shorter progression-free survival in sarcopenic patients [94].

Instead, only 2 studies have explored the correlation between sarcopenia and immunotherapy in patients with cirrhosis and HCC. In these studies, sarcopenia has been associated with a lower survival independently from confounders with median overall survival of 5 versus 14.3 months in sarcopenic versus non-sarcopenic patients [95, 96].

Management of Sarcopenia in Cirrhosis and HCC

No effective strategies have been developed or routinely used in clinical practice to treat sarcopenia in cirrhotic patients with HCC. Outside of any specific interventions, optimal management of underlying liver disease and

complications is primarily required. Nutrition and physical exercise represent the mainstay of current available strategies and are supported by several clinical studies (Fig. 2).

Nutrition and Supplementation

Dietary counselling should be a priority for all patients with cirrhosis and HCC. In any case, available meta-analyses have not been able to demonstrate an impact of nutritional supplementation on mortality [97] probably for the very short length of the studies. In a recent randomized-controlled trial (RCT), a 6-month intervention of guided dietary intake and monthly dietician visits in patients with decompensated cirrhosis and minimal HE, has shown an increase of muscle mass and strength and an improvement in minimal HE in the intervention group [98, 99]. In clinical practice, a key nutritional strategy includes small frequent meals with a late-night snack containing carbohydrates or proteins to reduce fat and protein catabolism, and improve nitrogen balance [100]. Even more important is the guidance of a dietician in the setting of sarcopenic obesity and decompensated cirrhosis where, at the same time, protein intake should be maintained and weight loss should be achieved [101].

While the role of an adequate protein intake has been clearly demonstrated, data supporting the use of BCAA are less consistent. Several studies have demonstrated that BCAAs improve the quality of life and reduce the incidence of HE [102, 103], but the largest meta-analyses of studies conducted in patients with encephalopathy have shown no impact on mortality [104]. In any case, guide-

lines recommend intake of BCAAs at the dose of 0.25 g/kg/day [99, 105]. Among BCAAs, leucine has demonstrated the greatest significant clinical benefit particularly through its active metabolite beta-hydroxy-beta-methylbutyrate [106, 107] that exerts anti-catabolic effects on skeletal muscles [107]. Oral leucine supplementation at a dose of 10 g/day, combined with physical activity, has been associated with an improvement of muscle mass and quality of life in cirrhotic patients after 12 weeks of supplementation [108]. A long-term administration of BCAA (12 g/day) for 2 years was associated with reduced levels of blood ammonia, reduced incidence of decompensation and better serum nutritional status and quality of life in cirrhotic patients [103]; however, no data about the impact on muscle mass and function were collected in this study.

In addition, relevant data derive from a RCT performed in patients with advanced solid cancers by Deutz et al. [109] in which the experimental group received a medical food containing 40 g protein, based on casein and whey protein and enriched with 10% free leucine compared to the control group receiving conventional food based on casein protein alone (24 g). Experimental supplementation induced a higher muscle protein synthesis overcoming the anabolic resistance to conventional medical food, observed in patients with advanced cancer. The interesting data on hydroxy-beta-methylbutyrate have been confirmed in patients with metastatic solid cancers whose supplementation with this nutrient was associated with increased lean body weight after 6 months of treatment with respect to controls [110].

Mitochondrial targeted antioxidants are another potential therapy to treat oxidative stress and restore protein synthesis [111]. Carnitine plays an important role in this metabolism and L-carnitine supplementation has demonstrated to prevent skeletal muscle mass loss in patients with cirrhosis after 1,000 mg/day administration for more than 6 months [112] and seems to have a dose-dependent effectiveness [113, 114]. Anyhow, not enough evidence has been developed in this context to recommend carnitine.

As regards to the role of cholecalciferol, while observational studies and mechanistic experiments clearly support a biological link between low vitamin D levels and the decline in muscle mass, strength and physical performance, and RCTs conducted to investigate the effect of oral vitamin supplementation to prevent or treat sarcopenia yielded conflicting results [115]. Indeed, while the association of cholecalciferol deficiency with CLD and mortality is known [116], its role in the treatment of sar-

copenia in cirrhosis has only marginally been evaluated. Recently, a small pilot RCT has been conducted in patients with decompensated cirrhosis (28% of patients with a history of HCC) that routinely received BCAA preparations, showing that vitamin D supplementation significantly increases muscle volume and grip strength after 12 months of treatment [117]. The small sample and the absence of a control arm without BCAA supplementation limit the results of the study but simultaneously confirm the suggested effective role of vitamin D supplementation in these patients. Therefore, currently available evidence remains limited in this field and vitamin D supplementation certainly maintains a key role only in the sustainment of an optimal skeletal health in oncological patients [118].

Lastly, the role of follistatin, a myostatin antagonist, is of particular interest in patients with cirrhosis and HCC, but even if some studies have already demonstrated a role for this molecule in stimulation of muscle mass and strength in preclinical studies [119] and an association between follistatin/myostatin levels and survival in patients with HCC [120], no clinical evidence have been developed. Moreover, for the heterogeneity and the small sample of the studies, no conclusive data and evidence have been developed for vitamin C, eicosapentaenoic acid, and docosahexaenoic acid supplementations [121].

Hormonal Treatment

Starting from the pathophysiological assumption of the reduced levels of testosterone in advanced liver disease, hormonal treatment has been evaluated in cirrhotic patients showing a significant improvement of muscle mass and bone mineral treatment [122]. Even though these promising results, many evidences suggest a role of testosterone in the development of HCC [123, 124] and therefore, it does not represent a useful tool in sarcopenia treatment in CLD and HCC.

Physical Exercise

Many recent studies have focused their attention on the benefits of physical exercise in patients with cirrhosis [125, 126]. The role of structured physical activity is confirmed by studies developed in patients with many types of cancer. For instance, progressive resistance exercises for 12 weeks improved lean body mass of 4.2% in patients with head and neck squamous cell cancer [127]. Most of the available data in liver disease derive from cirrhotic compensated patients, but no evidence has been produced on the impact on reversal of sarcopenia. In any case, it seems noticeable that, if possible, physical exercise

should be recommended to all patients with cirrhosis and with HCC in the early stages to prevent further loss of muscle mass [128]. Exercise has shown to improve muscle mass and strength, peak exercise capacity, fatigue, and hepatic venous pressure [129, 130]. Both walking 30 min three times per week and resistance exercise have shown to improve muscle mass in cirrhosis [131]. Studies conducted in patients with HCC subjected to locoregional treatment (mainly trans-arterial chemoembolization) have shown that exercise, alone or with supplementation with BCAAs, is associated with a lesser decrease of muscle mass during hospital stay or after 50 days from treatment with respect to controls [132, 133]. Finally, the role of physical exercise in patients awaiting LT has been only marginally evaluated [134] but no randomized clinical trials have been developed to assess its beneficial role on hospitalization and mortality. A preliminary care and safety assessment should be paid to identify patients with high risk of varices or HE (to optimize treatment and prophylaxis), to assess cardiopulmonary function and contextualize the best choices in patients under systemic active oncological treatment.

Conclusion

The evidence of such an important prognostic role of sarcopenia in CLD and HCC makes the clinician's interventions even more important since sarcopenia recognition and proactive treatment may significantly improve patients' outcomes. Particularly, in the context of HCC, sarcopenia evaluation requires an all-encompassing ap-

proach that takes into account not only cancer but primarily underlying CLD. Besides, future prospective studies with larger sample size and appropriate end points are urgently needed to provide more robust evidence about the prognostic role of sarcopenia in this specific setting and to verify the efficacy of nutritional, pharmacological, and non-pharmacological interventions in reversing sarcopenia.

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Conflict of Interest Statement

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