

Complete Pathological Response in Advanced Hepatocellular Carcinoma. Peek-A-Boo?

Sumou Ingrid Karmane^{1#*}, Hui Cheng Vai^{1#}, Kok Lai Fong², Chio Chan Fong², Chong Keng Sang³, José Costa-Maia^{4#}

Corresponding author:

*Sumou Ingrid Karmane, MD
Department of Oncology
Centro Hospitalar Conde
de São Januário, Macau, China
E-mail: ingridsumou@gmail.com

#These authors contributed equally

Open Researcher and Contributor
Identification (ORCID) numbers:
Sumou Ingrid Karmane (0000-0002-
4852-7405), Hui Cheng Vai (0000-
0003-3041-1794), Chio Chan Fong
(0000-0001-9804-2361), José
Costa-Maia (0000-0002-6363-3628)

¹Department of Oncology; ²Department of Pathology; ³Department of Radiology;
⁴Department of General Surgery
Centro Hospitalar Conde de São Januário, Macau, China

ABSTRACT

Spontaneous rupture of hepatocellular carcinoma (HCC) is a potentially lethal complication. Despite various treatment modalities with curative intent, there are scant data on ruptured cases achieving complete pathological response (pCR), with only a handful of case reports. We report a case of a Chinese male patient with large advanced HCC (aHCC) first detected with rupture in an emergency setting, developing a pCR after multidisciplinary onco-surgical approach.

Key words: hepatocellular carcinoma, rupture, complete pathological response

INTRODUCTION

HCC is a major problem worldwide, with an incidence of approximately 18.3 per 100,000 in China (1), thus posing a significant burden due to its large population. Tumor rupture with subsequent intraperitoneal hemorrhage is a life-threatening condition, and occurs in 3-15% of patients (2-6), often with high mortality rates and compromised survival (7).

Complete pathological response achieved by single modalities in aHCC is infrequent. Tyrosine kinase inhibitors (TKI) alone were reported to yield CR (no imaging evidence of neoplastic disease) in <1% of aHCC (8). In one meta-analysis of Transarterial chemoembolization (TACE), CR was 0% in nine of the 13 randomized control trials (RCTs) analyzed, with a mean CR of 6% (0.007-30%) in the remainder (9). The combination of immunotherapy with anti-angiogenesis has overturned the odds and became the standard therapy in aHCC, with an 8% CR rate (8). In a real world study from China, the combination of immunotherapy plus TKI yielded pCR in 5% of initially unresectable HCC patients (10). A consensus on the best treatment approach for this entity is still lacking. Therefore, multidisciplinary management is imperative.

CASE REPORT

In April 2020, a 60-year-old Chinese male patient was admitted to the

Received: 05.12.2022

Accepted: 18.02.2023

Emergency Department of our Center, following sudden onset of abdominal pain associated with significant distension and shock. He was a local dentist, unvaccinated for hepatitis B virus (HBV), with past medical history remarkable for pulmonary tuberculosis for which he had completed treatment 40 years previously. He denied alcohol intake, drug use, or transfusions. Laboratory examination revealed a hemoglobin level of 8.7 g/dl with a baseline reference of 14 g/dl. Serologic testing showed hepatitis B surface antigen positive, with a viral load of HBV-DNA 500,000 IU/mL, and an alpha-fetoprotein (AFP) level of 167 ng/mL. Computed tomography (CT) scan revealed a cirrhotic liver with a 12.9 cm x 11.6 cm hypodense mass in the right lobe with associated hemoperitoneum of moderate amount suggesting tumor rupture. The portal vein and the inferior vena cava were patent (*fig. 1*). Digital subtraction angiography (DSA) was performed, visualizing a large enhancing mass in the right hepatic lobe. Trans-arterial embolization (TAE) was performed and hemostasis was achieved. The patient gradually stabilized and started receiving tenofovir alafenamide, at a daily dose of 25 mg. Magnetic resonance imaging (MRI) as well as chest-abdomen-pelvis CT showed post TAE change of the right hepatic mass with no evident extrahepatic spread of the disease. At that point, he had a Child-Pugh class B score of 7, with an Eastern Cooperative Oncology Group (ECOG) performance score of 1. Multidisciplinary evaluation considered an advanced HCC not amenable to primary surgical resection, and decided for bridge treatment with sorafenib, started in June 2020. A control CT scan in Sept 2020 showed

tumor progression (*fig. 2*). The patient was deemed ineligible for antiangiogenic combination approach because of a variceal hemorrhage episode in October 2020. After discussion, immunotherapy with nivolumab, at a dose of 480 mg intravenously every 4 weeks was initiated in Nov 2020. After two cycles, his AFP level dropped from 258 to 10.4 ng/mL, and after four cycles, returned to the normal range (<7 ng/mL) (*fig. 3*). Serial imaging with CT scan showed favorable response with a slow but steady reduction of the previous mass in the right hepatic lobe and no new lesion in the remaining liver (*fig. 4*).

After further discussion, combination treatment with ipilimumab, at a dose of 1 mg/kg intravenously, along with nivolumab 3 mg/kg intravenously, was administered triweekly for two cycles. Considering further tumor reduction and absence of distant metastasis, he received surgical resection in Nov 2021. Intraoperative findings included a large tumor measuring 7 x 6.8 x 5.5 cm at the right hepatic lobe with intense adhesions to the right adrenal gland, right colic flexure and right border of the hilar plate including the gallbladder. There was no ascites. Right hemihepatectomy with en-bloc cholecystectomy was performed. Pathology revealed a well-demarcated mass limited to the liver, with complete necrosis and no identified viable tissue. The tumor was surrounded by dense fibrous tissue with old hemorrhage and infiltration of inflammatory cells, without evidence of vascular permeation. These findings confirmed a pCR (*fig. 5*). Nivolumab monotherapy was resumed 7 weeks after surgery, with the previous flat-dosing regimen of 480 mg intravenous once every 4 weeks. To date, his AFP

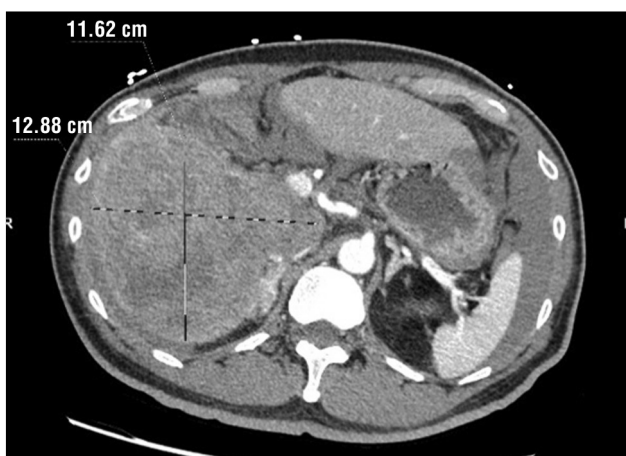


Figure 1 - CT showed a cirrhotic liver with a 12.9 cm x 11.6 cm hypodense mass in the right lobe with associated hemoperitoneum of moderate amount suggesting tumor rupture.

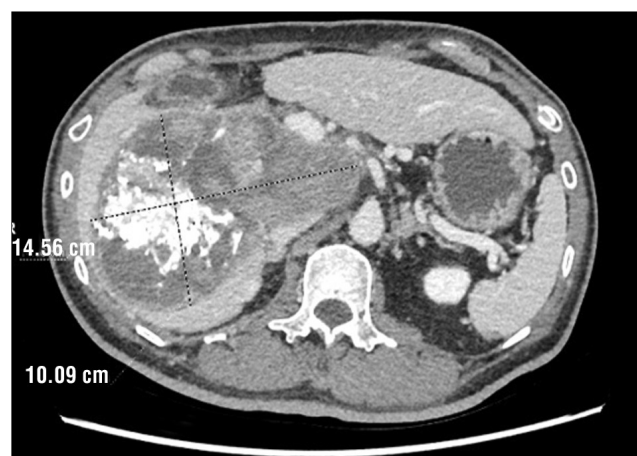


Figure 2 - Evidence of disease progression under sorafenib, with portal vein and IVC compression.

Figure 3 - The level of alpha-feto-protein (AFP) sharply descended after two courses of nivolumab, remaining normal after four cycles

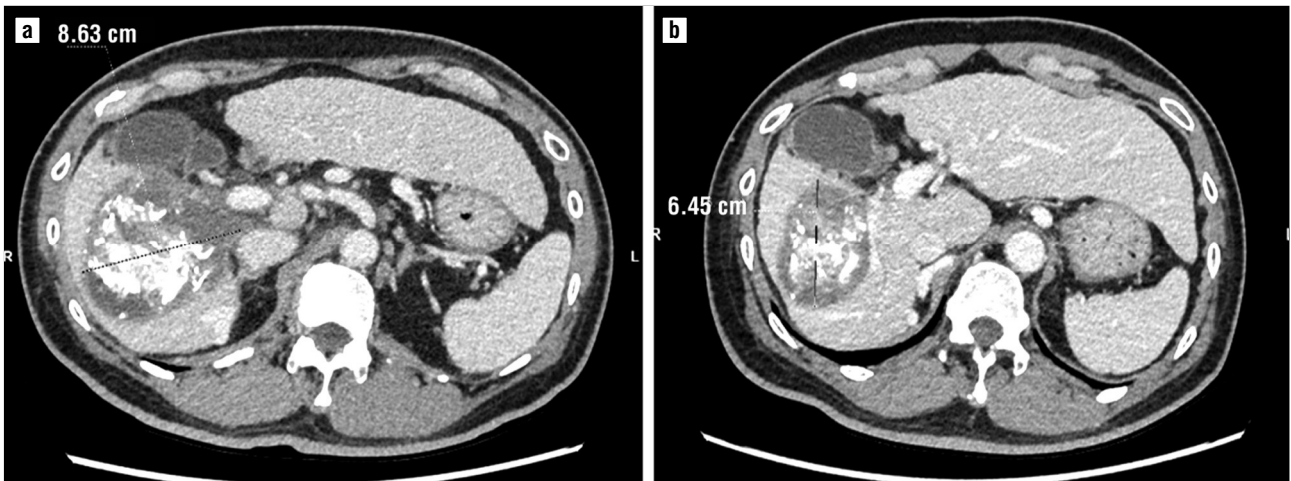
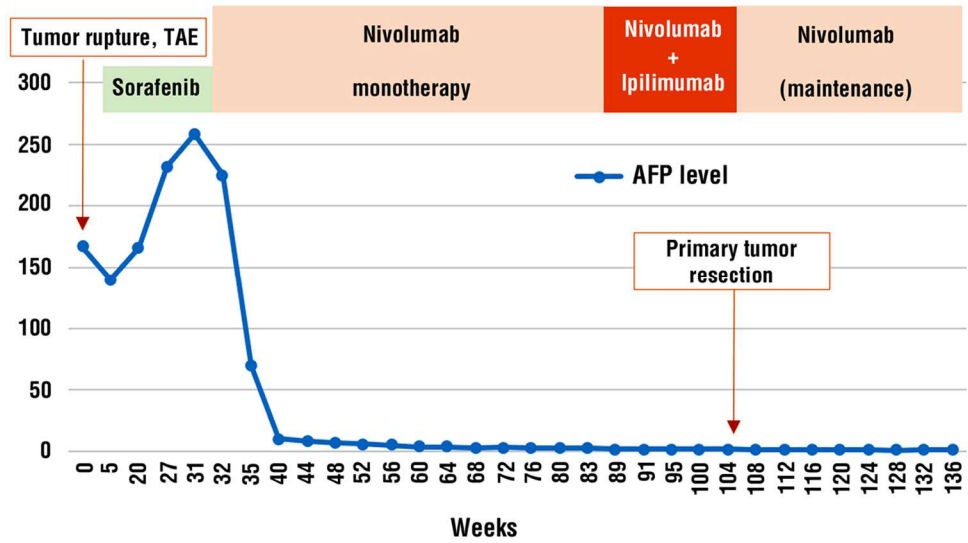


Figure 4 - (a) Partial response after six cycles of nivolumab monotherapy. The mass shrank to 8.6 cm. (b) Further tumor reduction to 6.4 cm after two cycles of dual immunotherapy with nivolumab plus ipilimumab.

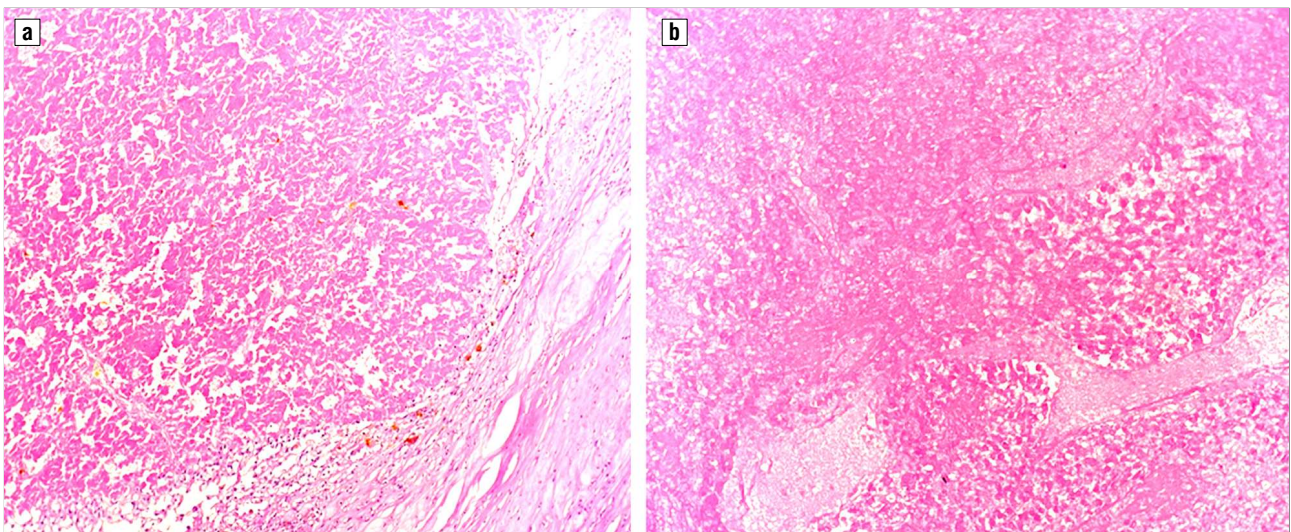


Figure 5 - Histologic section showing complete necrosis with no viable tissue (hematoxylin-eosin stain). (a) 100x (b) 200x.

level has remained in the normal range (*fig. 3*). The most recent post-operative CT scan in Sept 2022 showed no evidence of tumor recurrence or metastasis. The patient was still under the same maintenance treatment at the time of writing this report in Nov 2022.

DISCUSSION

Tumor rupture is a potentially lethal complication of HCC, with a higher incidence in Asia and Africa than in Europe (2, 3, 6, 11). A 10-years retrospective study observed a 9% incidence rate of spontaneous HCC rupture (7), with a one-month mortality rate reaching 38% (7). Spontaneous rupture ranks third in the leading causes of death due to HCC after tumor progression and liver failure (12), and, each year, is responsible for the death of almost 10% of HCC patients in Japan (13). Tumor rupture in HCC may lead to a high rate of peritoneal dissemination and has a negative impact on patient survival (14). Prognosis is generally poor in patients with ruptured HCC (15): two meta-analyses demonstrated spontaneous HCC rupture as a predictor of poor survival (16, 17), with significantly shorter overall survival (OS), (hazard ratio (HR), 1.65; 95% confidence interval (CI), 1.33–2.05) and disease free survival (DFS) (HR, 1.42; 95% CI, 1.12–1.80) (17).

Complete pathological response is an exceptionally rare occurrence in HCC, especially following tumor rupture (14). TKI alone were reported to yield CR in 0.4% of aHCC (18). In a few single case reports, immunotherapy with PD-1 inhibition alone or in combination with TKI, were reported to yield CR in aHCC (19–21). Two case reports in PubMed documented CR being achieved in aHCC treated with TACE followed by sequential application of PD-1 inhibition combined with TKI for conversion therapy. However, because surgical resection was not performed, pCR could not be confirmed (22). In one meta-analysis of immunotherapy for patients with aHCC who received PD-1/PD-L1 inhibition, CR was 0.01 (95% CI 0.01–0.03) in 20 single-arm studies; for patients who received monotherapy and combination therapy (with the addition of non-checkpoint-inhibitor agents, as well as platinum-based chemotherapy), CR was 0.02 (95% CI 0.01–0.04) vs 0.01 (95% CI 0.00–0.08) (23).

In the present case, the patient first received TAE for hemodynamic stabilization, inducing tumor necrosis and potential release of intratumoral antigens, for which the sequential application of checkpoint inhibition achieved an intensive immune response effect. For patients with aHCC refractory to sorafenib,

nivolumab had been granted accelerated approval by the Food and Drug Administration (FDA), and was proposed for our patient as valid option for a ruptured and bleeding tumor progressing under sorafenib. The patient developed a favorable response to nivolumab, that was continued in spite of the indication having been withdrawn by the pharmaceutical company because of insufficient data in a phase III study (24). Ipilimumab was subsequently added as a combination from Sept to Oct 2021, in reference to the clinical benefit reported in a phase III study (25). Follow-up CT scan showing further downsizing of the primary tumor and no evidence of distant metastasis, opened a window-of-opportunity for surgical resection, that the patient underwent with an uneventful recovery. Pathology confirmed complete tumor necrosis with no residual carcinoma. Presently he keeps maintenance nivolumab therapy with no evidence of tumor recurrence.

CONCLUSION

There is no consensus on the best treatment approach for this entity. Over the past couple of years, the rapid progress of molecular targeted therapy has expanded the therapeutic options for aHCC. Immunotherapy is being incorporated into HCC treatment, and the combination with molecular targeted therapy is emerging as a tool to enhance the immune response. The quest for biomarkers that may guide systemic therapy strategy by predicting treatment response, will be of paramount importance.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All subjects gave their informed consent for inclusion before participation. The study was conducted in accordance with the Declaration of Helsinki.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424.
2. Obeidat AE, Wong LL. Spontaneous rupture of hepatocellular carcinoma: new insights. *J Clin Exp Hepatol.* 2022;12(2):483–491.
3. Kerdasuknirun J, Vilaichone V, Vilaichone RK. Risk factors and prognosis of spontaneously ruptured hepatocellular carcinoma in

- Thailand. *Asian Pac J Cancer Prev*. 2018;19(12):3629-3634.
4. Zhu Q, Li J, Yan JJ, Huang L, Wu MC, Yan YQ. Predictors and clinical outcomes for spontaneous rupture of hepatocellular carcinoma. *World J Gastroenterol*. 2012;18(48):7302-7.
5. Spiliotis J, Nikolaou G, Kopanakis N, Vassiliadou D, Terra A, Efsthathiou E. Hepatocellular carcinoma peritoneal metastasis: role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Gulf J Oncolog*. 2017;1(24):20-23.
6. Vergara V, Muratore A, Bouzari H, Polastri R, Ferrero A, Galatola G, Capussotti L. Spontaneous rupture of hepatocellular carcinoma: surgical resection and long-term survival. *Eur J Surg Oncol*. 2000;26(8):770-2.
7. Liu CL, Fan ST, Lo CM, Tso WK, Poon RT, Lam CM, et al. Management of spontaneous rupture of hepatocellular carcinoma: single-center experience. *J Clin Oncol*. 2001;19(17):3725-32.
8. Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862-873.
9. Camma C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology*. 2002;224(1):47-54.
10. Xie D, Sun Q, Wang X, Zhou J, Fan J, Ren Z, et al. Immune checkpoint inhibitor plus tyrosine kinase inhibitor for unresectable hepatocellular carcinoma in the real world. *Ann Transl Med*. 2021;9(8):652.
11. Xia F, Ndhlovu E, Zhang M, Chen X, Zhang B, Zhu P. Ruptured Hepatocellular Carcinoma: Current Status of Research. *Front Oncol*. 2022;12:848903.
12. Sahu SK, Chawla YK, Dhiman RK, Singh V, Duseja A, Taneja S, et al. Rupture of Hepatocellular Carcinoma: A Review of Literature. *J Clin Exp Hepatol*. 2019;9(2):245-256.
13. Miyamoto M, Sudo T, Kuyama T. Spontaneous rupture of hepatocellular carcinoma: a review of 172 Japanese cases. *Am J Gastroenterol*. 1991;86(1):67-71.
14. Aoki T, Kokudo N, Matsuyama Y, Izumi N, Ichida T, Kudo M, et al. Prognostic impact of spontaneous tumor rupture in patients with hepatocellular carcinoma: an analysis of 1160 cases from a nationwide survey. *Ann Surg*. 2014;259(3):532-42.
15. Chan WH, Hung CF, Pan KT, Lui KW, Huang YT, Lin SY, et al. Impact of spontaneous tumor rupture on prognosis of patients with T4 hepatocellular carcinoma. *J Surg Oncol*. 2016;113(7):789-95.
16. Huang X, Jia C, Xu L, Bi X, Lai F, Huang Z, et al. Survival of Patients Subjected to Hepatectomy After Spontaneous Rupture of Hepatocellular Carcinoma: A Meta-analysis of High-quality Propensity Score Matching Studies. *Front Oncol*. 2022;12:877091.
17. Xu J, Hong J, Wang Y, Zhou L, Xu B, Si Y, He Y, et al. Prognostic Influence of Spontaneous Tumor Rupture in Patients With Hepatocellular Carcinoma After Hepatectomy: A Meta-Analysis of Observational Studies. *Front Surg*. 2021;8:769233.
18. Di Costanzo GG, Casadei Gardini A, Marisi G, Foschi FG, Scartozzi M, Granata R, et al. Validation of a Simple Scoring System to Predict Sorafenib Effectiveness in Patients with Hepatocellular Carcinoma. *Target Oncol*. 2017;12(6):795-803.
19. Mahn R, Vogt A, Kupczyk P, Sadeghlar F, van Beekum K, Hüneburg R, et al. Programmed cell death protein 1 (PD-1)-inhibition in hepatocellular carcinoma (HCC): a single center experience. *Scand J Gastroenterol*. 2020;55(9):1057-1062.
20. Zhong K, Xu Y, Cheng Y, Wen Y, Cai L, He G, et al. Case report: Primary hepatocellular carcinoma with portal vein tumor thrombus characterized by active tumor immune microenvironment achieving a complete response following treatment of combined immunotherapy. *Front Immunol*. 2022;13:999763.
21. Zhang W, Hu B, Han J, Wang Z, Ma G, Ye H, et al. Surgery After Conversion Therapy With PD-1 Inhibitors Plus Tyrosine Kinase Inhibitors Are Effective and Safe for Advanced Hepatocellular Carcinoma: A Pilot Study of Ten Patients. *Front Oncol*. 2021;11:747950.
22. Nong X, Zhang YM, Liang JC, Xie JL, Zhang ZM. Complete response by patients with advanced hepatocellular carcinoma after combination immune/targeted therapy and transarterial chemoembolization: two case reports and literature review. *Transl Cancer Res*. 2022;11(8):2973-2984.
23. Rao Q, Li M, Xu W, Pang K, Guo XB, Wang D. Clinical benefits of PD-1/PD-L1 inhibitors in advanced hepatocellular carcinoma: a systematic review and meta-analysis. *Hepatol Int*. 2020;14(5):765-775.
24. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23(1):77-90.
25. Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol*. 2020;6(11):e204564.