Recurrence of Cancer-associated Venous Thromboembolism between 2009 and 2013: A Nationwide Korean Study

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Purpose: Venous thromboembolism (VTE) is a frequent complication in patients with cancer, but the recurrence rate remains unclear in treatment of cancer-associated VTE (CAT). We examined the recurrence rates in patients with CAT and compared them with those of non-cancer-associated VTE (NCAT) patients in Republic of Korea.

Methods: We obtained medical claims data on patients with CAT and NCAT from the Health Insurance Review and Assessment (HIRA) database between 2009 and 2013, which included age, sex, and anticoagulant use history.

Results: Among 59,626 index cases, 19,725 (33.1%) had diagnostic codes for cancer and VTE. The proportions of male were 53.8% and 41.9%, and the proportion of pulmonary embolism (PE) with or without deep vein thrombosis (DVT) were 60.4% and 59.9% in CAT and NCAT group, respectively. The rate of recurrent VTE was significantly higher in the CAT than in the NCAT group (7.08% vs. 6.54%; relative risk [RR]: 1.083; 95% confidence interval [CI]: 1.017–1.153; P=0.013) despite a shorter duration of follow-up in the CAT patients. Upon subgroup analysis, the recurrent VTE rate in the CAT group was significantly higher than that in the NCAT group for patients ≥ 60 years of age (6.96% vs. 5.92%; RR: 1.177, 95% CI: 1.090–1.270; P<0.0001); in females (7.3% vs. 6.3%; RR: 1.144, 95% CI: 1.047–1.250; p<0.003); and in the PE group (7.7% vs. 6.8%; RR: 1.125, 95% CI: 1.041–1.216; P<0.003).

Conclusion: Recurrence rate in patients with CAT was significantly higher than that of NCAT patients. A subgroup analysis revealed that the recurrence rates in CAT versus NCAT were significantly increased in patients ≥ 60 years, in the PE group, and in the female group.

Keywords: Cancer, Venous thromboembolism, Pulmonary embolism, Deep vein thrombosis, Anticoagulants, Incidence, Recurrence

Introduction

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in patients with cancer irrespective of cancer stage. Two successive nationwide population-based epidemiologic studies conducted between 2004 and 2013 using the Korean Health Insurance Review and Assessment Service (HIRA) database1,2 showed a gradual increase in annual age- and sex-standardized incidence (ASR) of VTE over the decade, even though the incidence rates in Republic of Korea are lower than those in Western countries.2-4 Interestingly, recent studies have shown that, unlike the incidence rates, the recurrence rates of VTE in Asia are comparable to those in Western countries.4-7 Therefore, the recurrence rate of cancer-associated VTE (CAT) in Asia can be expected to be as high as that reported in a Western population but has not yet been reported. This study aimed to evaluate the recurrence rates of anticoagulant use in patients with CAT vs. non-cancer-associated thrombosis VTE (NCAT) using Republic of Korea HIRA data collected between 2009 and 2013.

Methods

Data acquisition

The Korean National Health Insurance (NHI) service, which is operated by the Ministry of Health and Welfare of Korea, covers the entire population of the Republic of Korea, making it a convenient resource for nationwide epidemiologic studies. The HIRA is a government-operated organization that conducts accurate review and quality assessment systems for NHI claims. Medical claims data contained within the HIRA include patient age, sex, diagnostic codes, and treatment information, including surgical history, prescribed drugs with doses and durations, and procedures. More detailed information regarding the HIRA database has been explained in previous studies.3,4 Access to HIRA data is regulated by the Rules for Data Exploration and Utilization of the HIRA; we obtained approval of the HIRA data access committee to use the data for this study. All data were delivered anonymously, which means that no researcher could access potentially identifiable personal information, including names, addresses, and dates of birth.

The HIRA collects claims data that healthcare service providers...
submit for reimbursement for services provided to patients. The HIRA database contains almost all hospital inpatient and community clinic outpatient data in Korea. Republic of Korea has a compulsory public health insurance coverage system (the NHI), which covers approximately 97% of the population. The remaining 3% of the population, which are covered by the National Medical Aid program, are also reviewed by the HIRA. Thus, a nationwide population study was feasible using this database. The number of people registered in the Korean NHI was 50,908,646 in 2011. This study was exempted from review by the Seoul National University Bundang Hospital Institutional Review Board (X-1608/360-901) due to its retrospective nature.

Definition of VTE and recurrence
A case was defined as VTE if both diagnostic and medication codes were identified in the same patient. In the current study, the term “VTE” was limited to patients with 1) deep vein thrombosis (DVT) of the lower extremity with diagnostic code I80.2 or I80.3 (embolism or thrombosis of the lower extremity) and 2) pulmonary embolism with diagnostic code I26 (pulmonary thromboembolism), I26.0 (pulmonary embolism with mention of acute cor pulmonale), or I26.9 (pulmonary embolism without mention of acute cor pulmonale). If a patient had both DVT of the lower extremity and PE, he/she was placed in the PE group. Therefore, the term “DVT” denotes “DVT of the lower extremity without PE”; “PE” means “PE with or without DVT,” and VTE is a combination of DVT and PE.

A recurrence was defined as follows: 1) if both VTE code and medication code were terminated and then simultaneously re-entered more than one month later; 2) if the medication codes were re-entered after the VTE code alone persisted without a medication code for more than one month; and 3) if the VTE code was re-entered in patients with an atrial fibrillation code after the medication code alone persisted without a VTE code.

Case identification
First, inpatient and outpatient cases with both diagnostic and medication codes for VTE from July 1, 2008, to June 30, 2014, were extracted from the HIRA data. The date of VTE diagnosis was defined as the first day of simultaneous assignment of both diagnostic and medication codes. We excluded patients who had been diagnosed with prevalent VTE before January 1, 2009, or incidental VTE between January 1, 2014, and June 30, 2014. Patients with venous

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**Fig. 1.** Overall flow of analyses for the study population obtained from HIRA data collected between 2009 and 2013. HIRA, Health Insurance Review and Assessment Service; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.
Thrombosis of the upper extremity, intra-abdominal venous thrombosis, or involvement of an unspecified site were excluded. Among the 64,165 identified cases (Population A), we excluded subsequent VTE cases (n = 981) that occurred in the same calendar year, resulting in an annual index of VTE cases (n = 63,184, Population B) (Fig. 1). We excluded all VTE cases (n = 3,358) in other calendar years between January 1, 2010, and December 31, 2013. Finally, 59,626 individuals with index VTE cases (Population C) were included (27,303 male, 45.8%) (Fig. 1).

Concurrent medication codes for unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or direct oral anticoagulant (DOAC, i.e., rivaroxaban) were mandatory to verify accurate detection of VTE. Diagnostic codes were assigned by physicians, and most codes were assigned in close proximity to the date of diagnostic imaging positive for VTE in both inpatients and outpatients. A case was defined as CAT if both a diagnostic code of cancer and a code of VTE were simultaneously present in the same patient.

### Treatment pattern

During the study period, the anticoagulants approved for VTE treatment in Republic of Korea included UFH, LMWH, DOACs, and warfarin. All medication codes for anticoagulants prescribed within six months of VTE diagnosis were collected from the HIRA databases. We analyzed anticoagulation patterns and classified them as follows: 1) UFH/LMWH regimen – use of UFH and/or LMWH without rivaroxaban or warfarin, 2) warfarin-based regimen – warfarin with UFH/LMWH, 3) rivaroxaban-based regimen – rivaroxaban only or rivaroxaban with UFH/LMWH but not with warfarin, and 4) mixed anticoagulation regimen – use of both rivaroxaban and warfarin within the initial six months of a VTE index event (Table 1).

### Statistical analysis

Crude annual recurrence rates (per 100,000 individuals) were determined using the number of individuals with recurrent DVT and/or PE as the numerator and the number of people in each group of VTE patients with cancer vs. without cancer in Population C as the denominator (Fig. 1). The ASR values of DVT and PE were directly adjusted to a mid-year population in 2011. The incidence rates and confidence intervals (CI) by age, sex, and year were estimated by Poisson distribution. The average annual percentage change in disease incidence was calculated as described previously (10). A P < 0.05 was considered statistically significant. The statistical analysis was performed using SAS Enterprise version 6.0.

### Results

Among 59,626 index VTE cases that occurred from January 2009 to December 2013, 19,725 (33.1%) had both a diagnostic code of cancer and a code of VTE (Fig. 1). In the CAT and NCAT groups, 53.8% and 41.9% of participants were male, and the incidence rates of PE ± DVT were 60.4% and 59.9%, respectively (Table 1). The rates of recurrent VTE were significantly higher in the CAT group than in the NCAT group (7.08% vs. 6.54%; relative risk [RR]: 1.083; 95% CI: 1.017–1.153; P = 0.013) despite a shorter duration of follow-up for the cancer patients. The median duration of follow-up was 1.57 years in CAT (95% CI: 1.47–1.67) and was not reached in NCAT patients. As age increased, the recurrence rate of VTE in CAT patients increased compared with that in NCAT patients (Fig. 2).

Upon subgroup analysis, the recurrent VTE rate in CAT patients was significantly higher than that in those with NCAT in patients ≥60 years of age (6.96% vs. 5.92%; RR: 1.177, 95% CI: 1.090–1.270; P < 0.0001); in females (7.3% vs. 6.3%; RR: 1.144, 95% CI: 1.047–1.250; P < 0.003); and in the PE group (7.7% vs. 6.8%; RR: 1.125, 95% CI: 1.041–1.216; P < 0.003) (Fig. 2).

The most common anticoagulant prescribed for patients with CAT was warfarin (53.1%), followed by LMWH (36.4%). The frequency of LMWH (36.4%) use in patients with CAT was twice that of NCAT patients (18.5%) (Table 1).

### Discussion

The recurrence rate of VTE was significantly higher in patients with cancer than in those without cancer (7.08% vs. 6.54%; RR: 1.083, 95% CI: 1.017–1.153; P = 0.013). This study confirmed that the recurrence rate in patients with CAT in Republic of Korea was comparable to those in Western populations, which suggests that there is no ethnic difference with regard to recurrence rates of CAT.

Prandoni et al. reported that the 12-month cumulative rate of recurrent thromboembolism during anticoagulant treatment was 20.7% (95% CI: 15.6–25.8) in cancer patients compared with 6.8% (95% CI: 3.9%–9.7%) in those without cancer, with a hazard ratio of 3.2 (95% CI: 1.9–5.4). The annualized risk of recurrent VTE after stopping therapy in patients with cancer was estimated to be 15%. The rate of recurrence was 9% and 7.2% in active cancer patients treated with dalteparin and tinzaparin in the CLOT and CATCH trials, re-

| Table 1. Baseline characteristics of the study population |
|-----------------------------------------------|
| **Type of anticoagulation N (%)**             | **Total VTEs** | **Cancer VTEs** | **Non-Cancer VTEs** | **P-value** |
| ---------------------------------------------|----------------|-----------------|---------------------|-------------|
| UFH/LMWH                                     | 18,791 (31.5) | 8,016 (40.6)   | 10,775 (27)         | <0.001      |
| Warfarin-based                                | 36,602 (61.9) | 10,481 (53.1)  | 26,121 (65.5)       | <0.001      |
| Rivaroxaban-based                             | 2,913 (4.9)   | 912 (4.6)      | 2,001 (5.0)         | 0.039       |
| Mixed regimen                                 | 1,220 (2.0)   | 316 (1.6)      | 904 (2.3)           | <0.001      |

DVT, deep vein thrombosis; PE, pulmonary embolism; UFH/LMWH, unfractionated heparin and/or low-molecular-weight heparin; VTE, venous thromboembolism.
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spectively.\textsuperscript{13,14} However, all these studies were performed in Western countries.\textsuperscript{11-15} Recently, Yhim et al. reported a cumulative risk of symptomatic recurrence of 5.9% and a rate of any recurrence of 7.6% in 124 patients treated with rivaroxaban for CAT in a prospective, multicenter, open-label study in Republic of Korea.\textsuperscript{16}

The ASR incidence rates of cancer in Republic of Korea have undergone a gradual increase from 210.5 to 290.5 per 100,000 in 1999 and 2013, respectively.\textsuperscript{17} Moreover, the incidence of cancer is high in older people.\textsuperscript{17} Many studies have reported that cancer patients have a four- to seven-fold higher relative risk of thrombosis than those without cancer.\textsuperscript{18} In addition, CAT is the second leading cause of death in cancer patients.\textsuperscript{19}

Although the incidence of CAT varies, this study showed that CAT accounted for 33.1% of all VTE episodes between 2009 and 2013. The recurrence rate in patients ≥ 60 years was significantly higher in CAT patients than in those with NCAT (6.96% vs. 5.92; RR: 1.177, 95% CI: 1.090–1.270; \(P<0.0001\)) (Fig. 2). These results suggest that the recurrence of VTE among cancer patients in the oldest age group will remain a challenge in terms of health cost in a society with an advanced age, which is expected in the near future in Republic of Korea.

The recurrence rate in female patients was significantly higher in CAT patients than those with NCAT (7.3% vs. 6.3%; RR: 1.144, 95% CI: 1.047–1.250; \(P<0.003\)) (Fig. 2). Louzada et al.\textsuperscript{20} validated the Ottawa score of being female as one of four independent factors predicting the risk of recurrent VTE in patients with CAT. Dullac et al.\textsuperscript{21} showed in their meta-analysis that the six-month pooled rate of recurrent VTE was 18.6% (95% CI: 13.9–23.9) based on Ottawa score. Consistently, our study found that being female was a risk factor for recurrence in patients with CAT. However, Girad et al.\textsuperscript{22} reported in their prospective cohort study that the Ottawa score failed to accurately predict recurrent VTE. Ahn et al.\textsuperscript{23} also failed to validate the Ottawa score in single-center, retrospective study. Among the variables, female sex showed no significant difference with a RR of 0.988 for recurrent VTE (95% CI: 0.624–1.565; \(P=0.958\)).\textsuperscript{23} Thus, additional research is needed to clarify whether the Ottawa score (including the female factor) can predict recurrent VTE in patients with CAT.

This study showed that physicians preferred warfarin-based anticoagulation (53.15%) over LMWH-based treatment (36.4%). Despite the relatively low cost of LMWH, warfarin-based treatments are prevalent among patients with CAT.\textsuperscript{2} Although Lee et al.\textsuperscript{13} showed that LMWH demonstrated lower VTE recurrence for patients with CAT compared with those treated with warfarin in the CLOT study, the trends in actual clinical practice might have a greater association with physician and/or patient preference. A similar pattern was observed in the United States (US), where less than half of patients with CAT received LMWH according to analyses of 2016 and 2017
US claims data.24,25 Nevertheless, the proportion of patients on LMWH was twice as high in the CAT group compared to the NCAT group (36.4% vs. 18.5%) (Table 1).

Recently, DOACs have emerged as a novel anticoagulant solution in that they can be administered at a fixed dose with minimal monitoring through a convenient oral route.26 Although injection of LMWH had effective outcomes in large major clinical trials,13,14 injection therapy for longer than three months can be inconvenient for some patients. Rivaroxaban has been covered by the Korean NIH service since January 2013 and quickly began to replace previously established anticoagulants. This study found that DOACs were prescribed for 4.6% of CAT patients within one year of launching. There is limited evidence from subgroup analyses of major randomized trials for use of DOACs for CAT.27 Recently, Mulder et al. reported in their meta-analysis that the risk of recurrent VTE with DOACs in patients with CAT was comparable to that of dalteparin therapy.28-31 Therefore, on the basis of these results, physicians are expected to increase prescription of DOACs in CAT patients.

There are several limitations to this study: (1) this is retrospective study; (2) it was not classified according to cancer activity; (3) types of cancers were not analyzed separately, although recurrence rates of VTE vary according to cancer type; and (4) in cohort or randomized controlled studies, cases that satisfy the definition of recurrent VTE were identified and analyzed. However, based on our definition of recurrence in this study, which used HIRA data, the incidence of recurrent VTE might have been overestimated. For instance, if patients with CAT resume anticoagulants more than 1 month after stopping medication due to bleeding complication, this case would be counted as VTE recurrence. In addition, (5) we were not able to analyze whether the quality of anticoagulation with warfarin was associated with better clinical outcomes; and (6) the recurrence rates were not calculated according to type of anticoagulants.

Conclusion

In conclusion, recurrence rate in patients with CAT was significantly higher than that of patients with NCAT. Our subgroup analysis revealed that the recurrence rate of CAT was significantly increased in patients ≥60 years of age, in the PE groups, and in female groups.

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References

1. Kim L, Kim JA, Kim S. A guide for the utilization of Health Insurance Review and Assessment Service National Patient Samples. Epidemiol Health. 2014;36: e2014008.
2. Hong J, Lee JH, Yhiem HY, Choi WI, Bang SM, Lee H, et al. Incidence of venous thromboembolism in Korea from 2009 to 2013. PloS one. 2018;13:e0191897.
3. Jang MJ, Bang SM, Oh D. Incidence of venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. J Thromb Haemost. 2011;9:85-91.
4. Lee CH, Lin LJ, Cheng CL, Kao Yang YH, Chen JY, Tsai LM. Incidence and cumulative recurrence rates of venous thromboembolism in the Taiwanese population. J Thromb Haemost. 2010;8:1515-23.
5. Nakamura M, Wang YQ, Wang C, Oh D, Yin WH, Kimura T, et al. Efficacy and safety of edoxaban for treatment of venous thromboembolism: a subanalysis of East Asian patients in the Hokusai-VTE trial. J Thromb Haemost 2015;13:1666-14.
6. Yamashita Y, Morimoto T, Toyota T, Shiomi H, Makiyama T, Ono K, et al. Asian patients versus non-Asian patients in the efficacy and safety of direct oral anticoagulants relative to vitamin K antagonist for venous thromboembolism: A systemic review and meta-analysis. Thromb Res 2018;166:37-42.
7. Hwang HG, Choi WI, Lee B, Lee CW. Incidence and Risk Factors of Recurrent Venous Thromboembolism after Pulmonary Embolism. Tuberipe Respir Dis (Seoul). 2019.
8. Jang MJ, Bang SM, Oh D. Incidence of pregnancy-associated venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. J Thromb Haemost 2011;9:2519-21.
9. Korean Statistical Information Service. https://kosis.kr/statHtml/statHtml.do?orgId=350&tblId=TX_35001_A001 Accessed July 5, 2021.
10. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. Stat Med 2009;28:3670-82.
11. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simionni P, Giolomini B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-8.
12. Kearon C, Akl EA, Cornerota AJ, Prandoni P, Bourmeaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e195S-94S.
13. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349:146-53.
14. Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Jonas MS, Jarner MF, et al. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Pa tients With Active Cancer: A Randomized Clinical Trial. JAMA 2015;314:677-86.
15. Prins MH, Lensing AWA, Prandoni P, Wells PS, Verhamme P, Beyer-Westendorf J, et al. Risk of recurrent venous thromboembolism according to baseline risk factor profiles. Blood Adv 2018;2:788-96.
16. Yhiem HY, Choi WI, Kim SH, Nam SH, Kim KH, Mun YC, et al. Long-term rivaroxaban versus a coumarin for the treatment of acute venous thromboembolism in patients with active cancer in a prospective multicenter trial. Korean J Intern Med. 2018. Epub 2018/05/24. doi: 10.3904/kjm.2018.097. PubMed PMID: 29788694.
17. Oh CM, Won YJ, Jung KW, Kong HJ, Cho H, Lee JK, et al. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2013. Cancer Res Treat 2016;48:436-50.
18. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer 2010;102 Suppl 1(Suppl 1):S2-9.
19. Khorana AA, Francis CW, Culakova E, Kuderer NM, Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Circulation 2012;126: 446-54.
20. Delluc A, Miranda S, Ester PD, Louzada M, Alatari A, Ahn A, et al. Accuracy of the Ottawa score in risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism: a systematic review and meta-analysis. Haematologica 2020;105:1436-42.
21. Girard P, Laporte S, Chapelle C, Falvo N, Falchero L, Charec N, et al. Failure of the Ottawa Score to Predict the Risk of Recurrent Venous Thromboembolism in Cancer Patients: The Prospective PREDICARE Cohort Study. Thrombosis and haemostasis. 2021. Epub 2021/04/ 21. doi: 10.1055/a-1486-7497. PubMed PMID: 3387 8800.
22. Ahn S, Lim KS, Lee YS, Lee JL. Validation of the clinical prediction rule for recurrent venous thromboembolism in cancer patients: the Ottawa score. Support Care Cancer 2013;21:2309-13.
23. Khorana AA, McCrue KR, Milentijevic D, Fortier J, Nelson WW, Laliberté F, et al. Current practice patterns and patient persistence with anticoagulant treatments for cancer-associated thrombosis. Res Pract Thromb Haemost 2017;1:14-22.
24. Khorana AA, Yannicelli D, McCrue KR, Milentijevic D, Crivera C, Nelson WW, et al. Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 2016;145:51-3.
25. Kim S-A, Yhun S-H, Bang S-M. Current Management of Cancer-associated Venous Thromboembolism: Focus on Direct Oral Anticoagulants. J Korean Med Sci 2019;34:e52.
26. Song AB, Rosovsky RP, Connors JM, Al-Samkari H, Cruvera C, Nelson WW, et al. Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 2016;145:51-3.
27. Song AB, Rosovsky RP, Connors JM, Al-Samkari H, Cruvera C, Nelson WW, et al. Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 2016;145:51-3.
28. Song AB, Rosovsky RP, Connors JM, Al-Samkari H, Cruvera C, Nelson WW, et al. Evaluation of US prescription patterns: Are treatment guidelines for cancer-associated venous thromboembolism being followed? Thromb Res 2016;145:51-3.
29. Young AM, Marshall A, Thirlwall J, Chapman O, Lok-
are A, Hill C, et al. Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D). J Clin Oncol 2018;36:2017-23.

30. Agnelli G, Becattini C, Meyer G, Munoz A, Huisman MV, Connors JM, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. N Engl J Med 2020;382:1599-607.

31. Mulder FI, Bosch FTM, Young AM, Marshall A, McBane RD, Zemla T, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. Blood 2020. Epub 2020/05/13. doi: 10.1182/blood.2020005819. PubMed PMID: 32396939.