

Rapid progression of carotid stenosis was rare in a large integrated healthcare system during an eight-year period

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ABSTRACT

Objective: Few studies have evaluated the rapid progression of carotid stenosis on a large scale. We created a custom software algorithm to analyze an electronic medical record database to examine the natural progression of carotid stenosis, identify a subset of patients with rapid progression, and evaluate the specific patient risk factors associated with this rapid progression.

Methods: Patients in a large integrated healthcare system who had undergone two or more carotid ultrasound scans from August 2010 to August 2018 were identified. We did not distinguish between those with an established carotid stenosis diagnosis and those with a screening ultrasound scan. We used our novel algorithm to extract data from their carotid ultrasound reports. The degrees of carotid stenosis were categorized as follows: level 1, 0% to 39%; level 2, 40% to 59%; level 3, 60% to 79%; level 4, 80% to 99%; and level 5, complete occlusion. The primary endpoint was rapid vs slow progression of carotid stenosis, with rapid progression defined as an increase of two or more levels within any 18-month period of the study, regardless of the date of the initial ultrasound scan. The association of the demographic and clinical characteristics with rapid progression was assessed by univariable and multivariable logistic regression.

Results: From a cohort of 4.4 million patients, we identified 4982 patients with two or more carotid ultrasound scans and a median follow-up period of 13.1 months (range, 0.1-93.7 months). Of the 4982 patients, 879 (17.6%) had shown progression of carotid stenosis. Only 116 patients (2.3%) had had progression to level 4 (80%-99% stenosis) from any starting level during a median of 11.5 months. A total of 180 patients (3.6%) were identified as experiencing rapid progression during a median follow-up of 9.9 months. The final multivariable analysis showed that younger age ($P < .01$), white race ($P = .02$), lower body mass index ($P = .01$), a diagnosis of peripheral arterial disease ($P = .03$), and a diagnosis of transient ischemic attack ($P < .01$) were associated with rapid progression.

Conclusions: Using a novel algorithm to extract data from >4 million patient records, we found that rapid progression of carotid stenosis appears to be rare. Although 17.6% of patients showed any degree of progression, only 3.6% had experienced rapid progression. Among those with any disease progression, 20.5% had experienced rapid progression. Although the overall incidence of rapid progression was low, patients with any progression might warrant close follow-up, especially if they have the associated risk factors for rapid progression. The custom software algorithm might be a powerful tool for creating and evaluating large datasets. (*J Vasc Surg* 2021;73:1623-9.)

Keywords: Algorithm; Carotid; Natural language processing; Progression; Rapid; Stenosis; Stroke

The current Society for Vascular Surgery guidelines suggest screening for asymptomatic carotid stenosis in a select group of high-risk patients with specific risk factors, because the presence of more severe carotid stenosis has correlated with greater stroke risk.^{1,2} The progression of carotid stenosis conveys an even greater stroke risk.^{3,4} Previous largescale studies have found that ~20% of patients with asymptomatic carotid

stenosis will experience disease progression within 10 years.⁵⁻⁸ Although the natural history of carotid stenosis has been well studied, relatively few data exist regarding patients who have experienced rapid progression of carotid stenosis, especially on a large scale.^{9,10}

Electronic medical records (EMRs) have become an integral part of delivering modern healthcare to patients. Despite some associated frustrations and limitations,

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EMRs have enabled both healthcare systems and physicians to deliver better care to patients because of features such as the ability to instantly share patient information among multiple remote hospitals. Another benefit of EMRs is the ability to access a large patient database to obtain pertinent data from multiple discrete specialties,^{11,12} such as sequential carotid duplex ultrasound scans ordered by primary care physicians.¹³ The diagnosis of carotid stenosis requires the expert interpretation of several key measurements and often requires additional commentary to support and contextualize the findings. This complexity presents a challenge in data extraction, because pertinent information is often not readily available from a simple database search. Unlike laboratory results, ultrasound reports are provided in multiple formats, often with critical data such as laterality and the degree of carotid stenosis buried in a paragraph of text.

To fully take advantage of our EMRs and evaluate rapid progression of carotid stenosis on a largescale, we created a custom software algorithm that allowed us to analyze an electronic data set of >4 million patients. We aimed to examine the natural progression of carotid stenosis over time using this novel algorithm to identify a subset of patients with rapid progression of carotid stenosis and evaluate the specific patient risk factors associated with rapid progression.

METHODS

Our large, integrated healthcare system includes data from >4.4 million patients, including basic demographics, diagnoses, encounters, medications, and procedure notes. We queried our data warehouse for all reports related to carotid duplex ultrasound scans for carotid stenosis. We used appropriate department-specific ordering codes for each specialty that conducts carotid ultrasound scans, including vascular surgery, cardiology, and radiology. We then filtered these reports to include only patients with two or more examinations during the 8 years of the study, from August 2010 to August 2018. We did not distinguish between those with an established carotid stenosis diagnosis and those with a screening ultrasound scan. Although our current EMR system (Epic Systems Corp, Verona, Wis) was not implemented until 2011, the vascular ultrasound results preceding 2011 were available for viewing in our system, with the reports saved and coded as multiline "laboratory results." For these patients, the standard demographics, relevant medications, health covariates, and diagnostic medical history were retrieved. The data points included clinical features such as age, antiplatelet use, statin use, and previous transient ischemic attack (TIA) or stroke.

Because of limitations in the structure of our database, free-text reports such as those attached to carotid duplex ultrasound scans are stored as individual lines

ARTICLE HIGHLIGHTS

- **Type of Research:** A multicenter, retrospective, cohort study
- **Key Findings:** From 4.4 million unique patients, 4982 patients with multiple carotid ultrasound scans were analyzed using a novel algorithm for carotid stenosis progression. Although 879 patients (17.6%) had demonstrated carotid stenosis progression, only 180 of the 4982 patients (3.6%) had experienced rapid progression. The associated risk factors included younger age, white race, lower body mass index, and the diagnosis of peripheral arterial disease and transient ischemic attack.
- **Take Home Message:** The overall incidence of rapid carotid stenosis progression was low (3.6%); however, patients who demonstrate any progression might warrant close follow-up.

separated by either a user-inserted carriage return or a limit of 256 characters. The algorithm orders and rejoins these report lines to reassemble the original report and then scans the reassembled report from top to bottom to identify the "impression," "findings," or "recommendations" headings. All text after the headings was extracted for further analysis. The results for each side of the bilateral carotid duplex ultrasound scans were separated. To detect laterality, the algorithm divides the "impression," "findings," or "recommendations" section of the report into individual sentences (detected as free text separated by the period character) or fragments (detected as free text separated by a carriage return) and scans each of these segments for laterality (right, left, bilateral, both sides). Typically, a carotid duplex ultrasound report will be separated into left and right sections. The findings of one laterality will be discussed, and then the reading physician will report on the contralateral findings. Therefore, if a segment does not contain laterality, the algorithm assumes the laterality of the previous segment, an assumption that captures the use of subheadings such as right and left.

Carotid stenosis was detected using a waterfall approach in which an alternate detection approach was attempted only for those segments in which the previous approach had failed, allowing most of the stenosis levels to be extracted using the most high-quality and efficient approach before resorting to approximate detection for the remainder. The first approach used regular expression sequences to search for the expected "[1-9]0 - [1-9]9" levels (ie, 40%-59%, 60%-79%). The secondary regular expression sequences allowed for nonstandard two-digit readings (eg, 60%-80%, 50%-60%) and exact single readings (eg, 72%, <20%). If the segment did not contain a numerical reading, the second approach was to scan for written numbers (eg,

Table. Univariable and multivariable association of demographic and baseline clinical characteristics with progression status

Baseline characteristic	Progression		Unadjusted		Adjusted	
	Slow (n = 4802)	Rapid (n = 180)	P value	OR ^a (95% CI)	P value	OR ^a (95% CI)
Age, years	71.2 ± 10.4	69.8 ± 9.1	.147	0.88 (0.75-1.04)	.001	0.73 (0.61-0.87)
Sex			.365			
NA	1159 (95.4)	56 (4.6)		–	–	–
Female	1826 (97.0)	57 (3.0)		0.85 (0.59-1.21)	–	–
Male	1817 (96.4)	67 (3.5)		1	–	–
Race					.028	
1, White	3319 (96.5)	121 (3.5)	1 vs 2	1.34 (0.87-2.07)	1 vs 2	1.11 (0.68-1.81)
2, Black	936 (97.4)	25 (2.6)	1 vs 3	0.61 (0.40-0.92)	1 vs 3	0.48 (0.28-0.83)
3, Other	491 (94.4)	29 (5.6)	2 vs 3	0.45 (0.26-0.78)	2 vs 3	0.43 (0.22-0.84)
BMI, kg/m ²	28.8 ± 5.8	27.4 ± 5.2	.001	0.78 (0.68-0.91)	.012	0.79 (0.66-0.95)
Diabetes	2227 (96.5)	80 (3.5)	.614	0.92 (0.69-1.25)	–	–
Antihyperglycemic therapy	1819 (96.1)	74 (3.9)	.373	1	–	–
Hyperlipidemia	3931 (96.3)	151 (3.7)	.527	1.14 (0.76-1.70)	–	–
Antihyperlipidemic therapy	3941 (96.1)	161 (3.9)	.014	1	–	–
Hypertension	4048 (96.3)	156 (3.7)	.430	1.19 (0.77-1.84)	.174	1.63 (0.77-3.46)
Antihypertensive agents	3378 (96.1)	136 (3.9)	.143	1	–	–
Ischemic heart disease	2606 (96.5)	95 (3.5)	.690	0.94 (0.70-1.27)	–	–
Myocardial infarction	608 (96.0)	25 (3.9)	.574	1.13 (0.74-1.73)	–	–
Peripheral vascular disease	4143 (96.1)	167 (3.9)	.017	1.97 (1.13-3.46)	.036	3.13 (1.04-9.4)
Antiplatelet therapy	3850 (96.1)	156 (3.9)	.038	1	–	–
Transient ischemic stroke	1171 (93.7)	78 (6.2)	<.001	2.37 (1.76-3.21)	<.001	1.96 (1.33-2.88)
Anticoagulant agents	2178 (95.3)	107 (4.7)	<.001	1	.125	1

BMI, Body mass index; CI, confidence interval; NA, not available; OR, odds ratio.
^aOR for age change in 10 units; OR for BMI change in 5 units; adjusted OR estimated at observed average for other covariates in model.

“twenty” to “thirty”). If the segment did not contain any numbers, the segment was scanned for a list of expert-assembled keywords and phrases that might denote assumed-normal status (eg, normal, no significant stenosis, occluded). Finally, a similar list of keywords was used to detect potential surgical intervention.

Each detected degree of carotid artery stenosis was recoded into one of five levels: level 1, 0% to 39%; level 2, 40% to 59%; level 3, 60% to 79%; level 4, 80% to 99%; and level 5, complete occlusion. When postoperative intervention was noted, that particular reading and any subsequent ultrasound scan were removed. To ensure the detection of surgical interventions, our algorithm identified all patients with variants of the words “endarterectomy,” “stent,” “operative,” and “surgery” in the reports. In the initial validation cycles, whenever we encountered a patient who had undergone endarterectomy but was not excluded, we adjusted the algorithm to identify it. Finally, we reviewed the records for all patients for whom the algorithm had decreased three or more levels to determine whether they had received an intervention but had not been properly discarded by the algorithm. If the degree of stenosis did not cleanly

meet into one of the five levels, the stenosis was classified by the highest reported level. Thus, if the stated range was 50% to 69%, the stenosis was categorized as level 3.

The degree of stenosis, final assigned stenosis level, and laterality data were compiled, along with the segment of source text from which the level had been extracted, to create a validation file. Throughout the algorithm design process, the updated validation file was randomly sampled to evaluate progress. The patients’ medical records were individually opened and compared against the validation file to ensure that the extracted data, including the degree of stenosis, stenosis level, and laterality, matched the source text. If any errors were encountered, the algorithm was edited to account for the error, and the process was repeated. The final validation demonstrated a sample accuracy of 98.5%. The remaining errors were typically the result of the algorithm’s inability to parse complex grammar.

The demographics and clinical characteristics potentially contributing to carotid stenosis were collected for all patients (Table). We defined our primary endpoint as rapid vs slow progression of carotid stenosis. We defined rapid progression as an increase of two or more levels

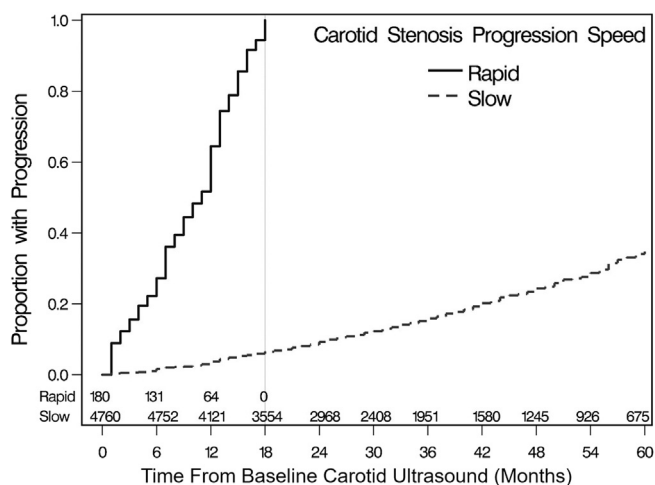


Fig. Proportion of patients with rapid vs slow progression of carotid stenosis stratified by time after baseline ultrasound scan. Rapid defined as progression of two or more levels within 18 months, and slow as no progression, progression of one level within 18 months, or progression of two or more levels after >18 months.

within any 18-month period of the study, regardless of the date of the initial ultrasound scan. Slow progression was then defined as any finding outside that parameter, which consisted of no progression, an increase of one level within 18 months, or an increase of two or more levels at >18 months. Slow progression could, therefore, also be considered as slow to no progression. The association of the demographic and clinical characteristics with progression of carotid stenosis was assessed by univariable and multivariable logistic regression with Firth correction to address potential data sparseness. A logistic regression analysis was performed as our endpoint of rapid progression was defined as a combination of events (progression of two or more levels) and period (any 18-month period). The intent of the present study was to consider the incidence of our event, rather than the point at which the progression had occurred.

The multivariable model was developed by including the main effects of all covariates available and subject to a liberal α of 0.2 to remain in the model by backward selection, while monitoring the Mallows Cp statistic and condition number. The potential correlation of the predictors in models were evaluated using the variance inflation factor, condition number, and tolerance. The largest variance inflation factor for all predictors was 1.9 and for the predictors in the final model was 1.3. The condition number for all predictors was 3.5 and for the predictors in the final model was 1.8. The smallest tolerance for all predictors was 0.51 and for the predictors in the final model was 0.76. The unadjusted and adjusted odds ratios and corresponding 95% confidence intervals were obtained. Because this was an observational study, the required sample size to power the study was not

calculated. Our goal was to determine the proportion of patients who had developed rapid progression through the creation of a custom algorithm that could extract these data from the EMRs. Furthermore, during our analysis, we were aware that the number of events (the number with rapid progression equaled 180) to be in check with a general rule of thumb of 10 events per predictor in a model.^{14,15} The maximum number of predictors in the adjusted model during backward selection was 16. We, therefore, consider that we had an adequate number of events per predictor (>10) in the model with the largest possible number of predictors. Analyses were performed using STAT, version 14.2 (SAS Institute, Cary, NC).

The hospital institutional review board reviewed and approved the study protocol.

RESULTS

Starting with an initial cohort of >4 million patients, the algorithm identified 4982 patients with two or more carotid duplex ultrasound scans during the 8-year period. A total of 9740 carotid arteries had undergone 29,363 ultrasound scans, for a median of two ultrasound scans per carotid artery (interquartile range, two to three). The median follow-up period was 13.1 months (range, 0.1-93.7 months). The patient demographics were recorded (Table). The mean age was 69.8 and 71.2 years, respectively, in the rapid and slow progression groups, with a 50% split between male and female patients. Most patients were white (69%). The patient characteristics and risk factors were also documented. Most patients had had a diagnosis of hyperlipidemia (81.9%), hypertension (84.4%), and peripheral arterial disease (PAD; 86.5%), and a few had had a diagnosis of diabetes (46.3%) or had experienced previous TIA (25.1%). Most patients had been receiving antiplatelet (80.4%) and anti-hyperlipidemic (82.3%) therapy.

During the study period, 4103 patients (82.4%) had not experienced any progression, and 879 patients (17.6%) had experienced some level of progression. We found that 639 patients (12.8%) had progressed by one level, 164 (3.3%) by two levels, 50 (1%) by three levels, and 26 (0.5%) by four levels. Only 116 patients (2.3%) had experienced progression to level 4 (80%-99% stenosis) from any starting level during a median period of 11.5 months. This group had had an average starting level of 2.1 (40%-59% stenosis). Additionally, 41 patients (0.8%) had experienced progression from level 3 to level 4 during the 8-year study period, and 37 patients (0.7%) had experienced progression from level 3 to level 4 within 18 months.

A total of 180 patients (3.6%) were identified as experiencing rapid progression, with progression of two or more levels within 18 months (Fig). The median follow-up time was 9.9 months. The results from the final multivariable analysis showed that younger age ($P < .01$), white

race ($P = .02$), lower body mass index (BMI; $P = .01$), a diagnosis of PAD ($P = .03$), and a diagnosis of TIA ($P < .01$) were associated with rapid progression. We did not find that the lack of antiplatelet therapy or anti-hyperlipidemic therapy were significant for progression, because these risks had been removed from the multivariable analysis during backward selection.

DISCUSSION

Using our custom software algorithm, we found that a few patients had developed rapid progression of carotid stenosis in a population of >4 million patients during an 8-year period. To the best of our knowledge, the present series is the largest to date evaluating the natural progression of carotid stenosis. The ability to analyze such a large number of patients was possible by the use of our algorithm, which created a data set that included all patient ultrasound scans performed in a large integrated healthcare system, not just those ordered by vascular surgeons. The present dataset included primary care physicians who order carotid duplex ultrasound scans but who, ultimately, do not refer the patient for evaluation by an interventionalist. As such, the data from these patients might never be entered into large databases such as the Vascular Quality Initiative or the National Surgical Quality Improvement Program.

Carotid duplex ultrasonography is a reliable and reproducible tool in the evaluation of carotid stenosis.¹⁶⁻¹⁸ A greater degree of carotid stenosis has been correlated with an increased risk of a cerebrovascular event.^{1,2} Multiple previous largescale studies have found that in patients with asymptomatic stenosis, ~20% will experience disease progression. In 1999, Muluk et al⁷ evaluated 1004 patients and found that 22.6% had developed some degree of progression within 10 years. In 2014, Kakkos et al⁴ examined 1121 patients and found that 19.9% had experienced progression within 8 years. They also noted that progression of carotid stenosis was predictive of major adverse cardiovascular events. They found that in 190 patients with progression of carotid stenosis and in 32 patients with progression to occlusion, 17.4% and 28.1%, respectively, experienced an ipsilateral ischemic event compared with 0% with regression and 10.3% with no change during a mean follow-up period of 4 years.

Although extensive data are available on the progression of carotid stenosis, relatively few data are available regarding rapid progression.^{9,10} Not only have no largescale studies been conducted, but also the term "rapid progression" itself has not been well established. Diomedi et al⁹ examined 571 patients with 50% to 69% carotid stenosis and defined rapid progression as progression to $\geq 70\%$ stenosis, near occlusion, or occlusion within 12 months. They found that 25% of patients had experienced rapid progression.⁹ In contrast, Sabeti et al¹⁰ reviewed 1065 patients with asymptomatic

carotid disease and noted that 93 patients (9%) had developed any progression of stenosis within 9 months. Of these 93 patients, 40% had experienced major adverse cardiovascular events during a median follow-up of 3.2 years.¹⁰ We chose an 18-month interval for rapid progression to include patients who might have been late with their scheduled 12-month carotid surveillance ultrasound scan. We did perform separate analyses of the data using both 12- and 18-month intervals for the definition of rapid progression and did not find significant differences in the incidence of rapid progression. We found that of the 4982 patients with multiple carotid ultrasound scans, 879 (17.6%) showed some degree of progression, consistent with the findings from previous largescale studies.^{4,7} However, we found that only 180 patients (3.6%) had experienced rapid progression, with progression of two or more levels within 18 months. This overall incidence of rapid progression was significantly less than that previously described.^{9,10} However, those previous studies had counted any degree of progression as rapid. However, we included only patients in whom progression had encompassed two or more levels. In addition, with the ability to study far more patients by datamining the EMRs, we started with a much larger cohort of patients who had undergone multiple ultrasound scans and, thus, a larger denominator that was likely not captured by other studies. However, of the among patients in our study with any level of progression, 20.5% had experienced rapid progression.

We identified younger age, white race, lower BMI, the diagnosis of PAD, and the diagnosis of TIA as risk factors for rapid progression. Previous studies have found that hypertension, coronary artery disease, chronic kidney disease, and diabetes had correlated with the progression of carotid stenosis.¹⁹⁻²¹ However, we did not find these to be statistically significant risk factors for rapid progression. The lack of antiplatelet use and statin use were also not statistically associated with rapid carotid progression, although the use of both have been well established as optimal medical therapy for the management of carotid stenosis. Although this lack of statistical significance might represent the inherent limits of querying an EMR database for such clinically meaningful factors, Conrad et al¹⁹ found that optimal medical therapy did not prevent the progression of carotid stenosis or the development of ipsilateral symptoms in patients with asymptomatic moderate (50%-69%) carotid stenosis within a 5-year period.

Because we were not able to correlate the occurrence of rapid progression with the incidence of symptom development, it is difficult for us to recommend a follow-up interval. As is modern practice, if a patient with a life expectancy >3 years experiences progression to asymptomatic >80% stenosis, either prophylactic intervention for stroke prevention or enrollment in the CREST-2 would be indicated.

Although EMR use has been linked with physician burnout,²² we have demonstrated a positive and novel use of this technology to understand the natural history of a disease. We created a custom software algorithm to extract data from reports written in paragraph form in a number of different formats. This algorithm creates the ability to efficiently and effectively convert text into data points, making it possible to examine patient data sets that in the past would have been prohibitively large owing to the requirement for manual review and entry into a database. For our study, we identified 4982 patients with multiple carotid ultrasound scans from an initial cohort of >4 million, extracted all pertinent information into a database, and analyzed the extracted data.

Previous groups have described the development of a natural language processing algorithm to potentially evaluate large databases.^{11-13,23} These studies served as a proof of concept, showing that the method was viable, often by comparing the results of the natural language processing algorithm against billing codes. However, to the best of our knowledge, no study has yet used an algorithm to mine the EMRs of a large healthcare system to create a database for analysis, especially for vascular disease.

Future directions include analyzing our current data to predict which patients will experience rapid progression of carotid stenosis. Additionally, future studies that use a similar algorithm and incorporate carotid plaque composition characteristics might yield important insights into the influence of carotid plaque composition on carotid stenosis progression. Another step will be to expand the algorithm to evaluate and incorporate data from multiple healthcare systems and to adapt the custom software algorithm to examine other disease processes such as peripheral arterial disease PAD or abdominal aortic aneurysms.

One limitation of our study was that it was a retrospective study from a single healthcare system. We also relied on physician documentation of clinical risk factors to be accurate. It is possible that patients who would have demonstrated progression had undergone ultrasound examinations outside of our hospital system or were lost to follow-up. Another limitation of our large data set was that we were unable to determine whether those with rapid progression will experience a greater incidence of symptom onset. We were also unable to accurately assess active smoking status because of how smoking status is coded in the EMRs. Hence, we could not confidently assess whether the patients included in the present analysis were active smokers. Finally, it is possible that our algorithm did not capture certain patients or was unable to parse very complex ultrasound reports.

CONCLUSIONS

Using a novel algorithm to extract data from >4 million patient EMRs, we found that rapid progression of carotid stenosis appears to be rare. Although 879 patients (17.6%)

had showed any degree of progression, only 180 patients of the 4982 patients (3.6%) had experienced rapid progression. We identified younger age, white race, lower BMI, a diagnosis of PAD, and a diagnosis of TIA as risk factors for rapid progression. Of the patients who had experienced any disease progression, 20.5% had experienced rapid progression. Although the overall incidence of rapid progression was low, patients who demonstrate any progression might warrant close follow-up, especially if they have the associated risk factors for rapid progression. The custom software algorithm might be a powerful tool for creating and evaluating large data sets.

AUTHOR CONTRIBUTIONS

Conception and design: CC, DF, TH, CL, CB, WS, HB

Analysis and interpretation: CC, DF, CVG, HB

Data collection: CC, DF, HB

Writing the article: CC, DF, CVG, HB

Critical revision of the article: CC, DF, CVG, TH, CL, CB, WS, HB

Final approval of the article: CC, DF, CVG, TH, CL, CB, WS, HB

Statistical analysis: CVG

Obtained funding: Not applicable

Overall responsibility: CC

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