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Criteria for follow-up of thyroid nodules diagnosed as follicular neoplasm without molecular testing – The experience of a high-volume thyroid centre in Japan

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Abstract

Background: Clinical management of follicular neoplasms (FNs) using molecular testing of thyroid-aspirated materials is not routinely performed in Japan. This article aims to identify low-risk FN nodules that can be followed up without molecular testing.

Methods: The relationship between preoperative findings, factors influencing surgical decision, and the risk of malignancy (ROM) was examined in 356 thyroid nodules with cytological diagnosis of FN at Kuma Hospital from January to December 2020.

Results: ROMs of FN with cytology results favouring malignancy (41.2%) were significantly higher than those favouring benign (7.7%) or borderline (8.2%) ($p < .001$). Moreover, ROMs of FN with ultrasonography results of high suspicion (54.5%) were significantly higher than those with low (4.5%) or intermediate suspicion (0%) ($p < .0001$). There was a large difference in overall ROM in tumours bordering 30 mm in size (<30 mm; 3.6%, ≥30 mm; 20.0%). ROMs of FNs with a tumour volume doubling rate (TVDR) of 1.0/year or more (28.6%) were higher than those of FNs with a lower TVDR (9.9%) ($p < .05$). The ROMs of FNs with or without one or more of the following four findings suggestive of malignancy: cytological findings favouring malignancy, ultrasonography findings of high suspicion, tumour size ≥30 mm, and TV-DR ≥1.0/year, were 14.6% and 1.0%, respectively.

Conclusion: FNs with no cytological findings favouring malignancy, no ultrasonography findings of high suspicion, tumour size <30 mm and TV-DR <1.0/year, are considered low risk and can be followed up without the need for molecular testing.

KEYWORDS
follicular neoplasm, molecular testing, risk of malignancy, thyroid, tumour volume-doubling rate

1 | INTRODUCTION

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was proposed as a reporting system for thyroid fine-needle aspiration cytology (FNAC) specimens in 2007 and described the recommended clinical management and risks of malignancy (ROMs) for each diagnostic category.[1] The TBSRTC was subsequently revised in 2017,[2] inspired by new developments, including molecular testing using aspirated materials and the reclassification of the encapsulated noninvasive follicular variant of papillary carcinoma as a noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). In 2007, the recommended management of follicular neoplasm (FN) nodules was surgical excision of the lesion, most often a hemithyroidectomy or lobectomy.[1] In the 2017 revision of the TBSRTC, molecular testing prior to surgery was incorporated as an option for the clinical management of FN nodules.[2] Molecular testing is necessary for good outcomes in the diagnosis and treatment of thyroid nodules, although gene panel testing is expensive and not universally available. Therefore, triage—without molecular testing—of patients with indeterminate thyroid nodules is the key to reducing unnecessary surgical intervention in locations where genetic testing is not available.

The diagnostic criteria and clinical management of the revised TBSRTC have been widely adopted in all countries. In Japan, however, the pathological classification and clinical management of thyroid tumours is different from that in the West, and different reporting systems are used.[3,4] As NIFTP has not been formally adopted as a disease entity in the Japanese thyroid pathology diagnostic code,[4] most NIFTP cases have been diagnosed as follicular adenoma.[5] In Japan, as the incidence of malignancy in *cyst fluid only* (CFO) nodules was extremely low (0.2%), CFO nodules are regarded as an *adequate specimen* and categorised independently.[3] In addition, molecular testing using aspirated materials is not routinely performed because it is not commercially available and is extremely expensive. Nevertheless, approximately half of FN nodules have been followed up without resection.[3] In cases of low-risk papillary thyroid microcarcinoma, the option of active surveillance without resection is available.[6] In addition to molecular testing, we believe it is possible to establish parameters that contribute to the clinical management of FN nodules. Based on the experience of a high-volume thyroid centre in Japan, where more than 7000 thyroid FNACs are performed annually, we tried to determine the conditions of FN nodules that could be followed up. This article aims to find FN nodules with low ROM without molecular testing; the results will serve as a reference for many institutions where molecular testing is not available.

2 | MATERIALS AND METHODS

Patients and clinical investigation: FNAC was performed for 7073 thyroid nodules at Kuma Hospital from January to December 2020. According to original reports, these were categorised as follows: unsatisfactory, 350 (4.9%); cyst fluid, 489 (6.9%); benign, 4603 (65.1%); undetermined significance, 304 (4.3%); FN, 356 (5.0%); suspicious for malignancy, 101 (1.4%); and malignant, 870 (12.3%). Among them, 356 nodules classified as FN were included in this study. Clinical data were obtained from the medical records of the Kuma Hospital. Diagnostic criteria for FN nodules were based on the revised TBSRTC.[2] There were no cases of preoperative molecular testing using aspirated materials. Levels of serum thyroglobulin greater than 1000 ng/ml were designated as high, and those below that were designated as low.

Ultrasound characteristics and classification: Tumour size was defined as the maximum diameter of the tumour recorded during preoperative ultrasonography and the reports were classified into three categories: low suspicion, intermediate suspicion, and high suspicion, corresponding to ultrasound classification (USC) 2.5 or less, USC 3.0, and USC 3.5 or more of USC system used at Kuma Hospital, respectively.[7] Findings suggesting high suspicion category included tumour thrombus, tumour protrusion extending from the main tumour, and nodules in the nodule.[8,9]

Cytomorphological findings and classification: Based on cytological findings, FNs were subdivided into favour benign, borderline, and favour malignant categories.[3] FNs with none, one, or two or more of the five cytological findings suggestive of malignancy, including dense follicles, three-dimensional microfollicles, trabecular arrangement, hyperchromasia, and enlarged nuclei, were classified as benign, borderline, or malignant, respectively (Figure 1).[10]

Tumour volume-doubling rate (TVDR): TVDR was used as a measure of tumour enlargement during follow-up.[11] The doubling rate was the inverse of the doubling time and was calculated based on the change in tumour size and its duration, as determined by ultrasonography. A doubling rate of 1.0/year or more was considered rapid growth.

Statistical analyses: Statistical analyses were performed using Stat Flex v.6 statistical software (Artech Co. Ltd., Osaka, Japan). Values of $p < .05$ were regarded as statistically significant in the Fisher probability test, Pearson's chi-square test, or Student's t-test.

3 | RESULTS

Among the 356 FN nodules, 158 (44.4%) were surgically resected, and the remaining 198 (55.6%) were followed up. Table 1 shows the findings that resulted in resection. The most common findings were cytological findings (91.1%), followed by tumour size (74.1%), ultrasonography findings (38.6%), and enlargement during follow-up (11.4%).

Table 2 shows the histological diagnoses of resected nodules. They included 14 (8.9%) adenomatous nodules, 91 (57.6%) follicular adenomas, 28 (17.7%) borderline tumours, and 25 (15.8%) malignant tumours. Sixteen NIFTP nodules (10.1%) were included as borderline tumours. The overall ROM was 7.0%. Follicular carcinoma constituted 64.0% of malignant nodules, and the remaining were a combination of well-differentiated carcinoma, not otherwise specified, poorly differentiated carcinoma, and papillary carcinoma. Of the 144 neoplastic lesions, 38 (26.4%) were oxyphilic cell variants.

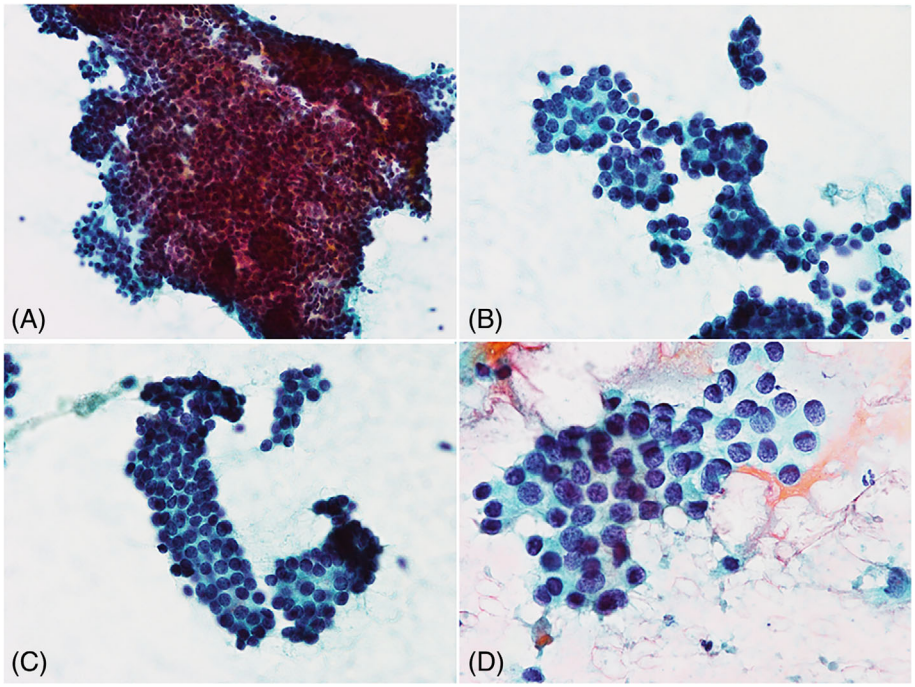

FIGURE 1 Five cytological findings suggestive of follicular carcinoma. (A) dense follicles; (B) three-dimensional microfollicles; (C) trabecular arrangements; (D) hyperchromasia and enlarged nuclei. (Papanicolaou staining, (A) ×4; (B, C) ×20; (D) ×40) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Findings that resulted in the resection of 158 resected follicular neoplasm nodules

Findings	Nodules (%)
Cytological findings	144 (91.1%)
Tumour size	117 (74.1%)
Ultrasonography findings	61 (38.6%)
Enlargement during follow-up	18 (11.4%)
Association with another nodule to be resected	10 (6.3%)
Symptoms due to pressure	2 (1.3%)
Cosmetic reasons	2 (1.3%)
Multiple follicular neoplasms	2 (1.3%)
Plummer's disease	1 (0.6%)
Extension into the mediastinum	1 (0.6%)
Elevated thyroglobulin level	1 (0.6%)
Patient's wish	1 (0.6%)

TABLE 2 Histological diagnoses of 158 resected nodules

Adenomatous nodule	14 (8.9%)
Follicular adenoma (*Oxyphilic cell variant*: 25)	91 (57.6%)
Follicular tumour of uncertain malignant potential (*Oxyphilic cell variant*: 4)	12 (7.6%)
Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)	16 (10.1%)
Follicular carcinoma (*Oxyphilic cell variant*: 8)	16 (10.1%)
Papillary carcinoma (*Oxyphilic cell variant*: 1, *follicular variant*: 1)	2 (1.3%)
Poorly differentiated carcinoma	2 (1.3%)
Well-differentiated carcinoma, not otherwise specified	5 (3.2%)

We examined the non-oxyphilic and oxyphilic types separately. Table 3 shows the resection rates (RRs) and ROMs in the 239 non-oxyphilic FN nodules. FN nodules that were found to favour malignant following cytological examination were more frequently resected than those found in the benign or borderline categories, but there was no statistically significant difference in the RR. The ROMs of FNs with a cytology result favouring malignancy were 58.3% and 41.2% in resected and overall cases, respectively. These frequencies were significantly higher than FN frequencies, in the favour benign and borderline categories (resection, $p < .05$; overall, $p < .001$). The RR of FN with an ultrasonography result of high suspicion was 90.9%, while the ROMs of the resected and overall cases were 60.0% and 54.5%, respectively. Both RR and ROMs were statistically significant compared with those in the low- and intermediate-suspicion categories (RR, $p < .05$; ROMs, $p < .0001$). RR and overall ROM increased with tumour size (RR, $p < .0001$; ROM, $p < .01$). Small FN nodules were frequently followed up and exhibited extremely low overall ROM (≤ 10 mm; 0%, 11–20 cm; 1.5%). Tumours bordering 30 mm in size showed large differences in overall ROM (<30 mm; 3.6%, >30 mm; 20.0%). Doubling rates were measured in 159 patients with FN, and 28 (17.6%) of these showed rapid growth. ROMs of FNs with rapid growth (28.6%) were significantly higher than those with slower growth (9.9%) ($p < .05$). FNs with high serum thyroglobulin (≥1000 ng/ml) were observed in 13 cases (5.8%), and these were more frequently resected than those with low serum thyroglobulin (<1000 ng/ml). However, there was no significant difference between the ROMs of FNs with high serum thyroglobulin compared to those with low serum thyroglobulin.

TABLE 3 Resection rates and risks of malignancy (ROM) in 239 non-oxyphilic cell follicular neoplasm nodules

	Resection rates	*p*-value	ROM/Resection	*p*-value	ROM/Overall	*p*-value
Cytology (239)						
Favour benign (26)	46.2% (12)	NS	16.7% (2)	<.05[b]	7.7%	<.001[b]
Borderline (196)	47.4% (93)		17.2% (16)		8.2%	
Favour malignant (17)	70.6% (12)		58.3% (7)		41.2%	
Ultrasonography (237)						
Low suspicion (66)	39.4% (26)	<.05[b]	11.5% (3)	<.0001[b]	4.5%	<.0001[b]
Intermediate suspicion (160)	50.6% (81)		0% (0)		0%	
High suspicion (11)	90.9% (10)		60.0% (6)		54.5%	
Size (238)						
≤10 mm (12)	16.7% (2)	<.0001[b]	0% (0)	.5322	0%	<.01[b]
11 to 20 cm (68)	25.0% (17)		5.9% (1)		1.5%	
21 to 30 cm (58)	37.9% (22)		18.2% (4)		6.9%	
31 to 40 cm (52)	67.3% (35)		31.4% (11)		21.2%	
≥40 mm (48)	85.4% (41)		22.0% (9)		18.8%	
Doubling rate (159)						
<1.0 (131)	58.8% (77)	<.05[a]	16.9% (13)	NS	9.9%	<.05[a]
≥1.0 (28)	82.1% (23)		34.8% (8)		28.6%	
Thyroglobulin (226)						
<1000 ng/ml (213)	46.0% (98)	<.005[a]	20.4% (20)	NS	9.4%	NS
≥1000 ng/ml (13)	92.3% (12)		25.0% (3)		23.1%	
Total (239)	49.0% (117)		18.8% (22)		9.2%	

Abbreviation: NS, not significant.
[a]Fisher's exact test.
[b]Pearson's chi-square test.

Table 4 shows RRs and ROMs in 117 oxyphilic cell FN nodules. The RR of FNs with a cytology result favouring benign was slightly higher than that of non-oxyphilic ones. Two patients with ultrasonography findings of high suspicion declined to undergo surgical resection. With regard to tumour size, there was a large difference in overall ROM in tumours bordering 30 mm (<30 mm, 1.2%; >30 mm, 21.9%). One of the 17 oxyphilic cell FN nodules sized ≤10 mm was resected, and the histological diagnosis suggested an adenomatous nodule. There was no evidence suggesting rapid growth and high serum thyroglobulin were related to increased ROM.

Table 5 shows the RRs and ROMs based on four findings suggestive of malignancy, which are cytological findings favouring malignancy, ultrasonography findings of high suspicion, tumour size ≥30 mm, and TVDR ≥1.0/year. ROMs increased with the number of findings. FN without any of the four findings (55.6%) showed a ROM of 1.0%, while FN with one or more of the four findings showed a ROM of 14.6%.

4 | DISCUSSION

To make a definitive diagnosis, the recommended management of a patient with a cytological diagnosis of FN is surgical resection. However, molecular testing prior to surgery may be used to further assess the risk of malignancy.[2] Given its high negative predictive value, molecular testing is used as an exclusion test, and clinical follow up without resection is recommended for FN nodules in the benign or low risk categories.[12–14] Molecular testing can avoid unnecessary surgery in *low risk* nodules, but not all facilities that perform thyroid FNAC can afford to perform molecular testing. In fact, there are no institutions that perform molecular testing on aspirated materials in Japan. Despite this, not all FN nodules were resected. We performed immediate resection of FN nodules considered to be at high risk but chose to follow up on other cases.[15] As a result, approximately half of the FN nodules were closely monitored without surgical resection.[3] By analysing our data, we were able to select FN nodules that could be followed up without molecular testing. This study proposes four findings suggestive of malignancy to identify FN nodules that can be followed up without molecular testing or resection. These are cytological findings favouring malignancy, ultrasonography findings of high suspicion, tumour size of 30 mm or more, and tumour volume-doubling rate of 1.0/year or more.

The distinction between follicular adenoma and follicular carcinoma is based on histological and clinical findings such as vascular invasion, capsular invasion, and metastasis. It is, therefore, theoretically impossible to distinguish between the two based on cytological specimens, and such cases are categorised as FN. In 1996, however, the Papanicolaou Society recommended that FN nodules be classified

TABLE 4 Resection rates and risks of malignancy (ROM) in 117 oxyphilic cell follicular neoplasm nodules

	Resection rates	*p*-value	ROM/Resection	*p*-value	ROM/Overall	*p*-value
Cytology (117)						
Favour benign (4)	50.0% (2)	<.05[b]	0% (0)	NS	0%	<.05[b]
Borderline (104)	30.8% (32)		15.6% (5)		4.8%	
Favour malignant (9)	77.8% (7)		42.9% (3)		33.3%	
Ultrasonography (115)						
Low suspicion (51)	19.6% (10)	<.01[b]	0% (0)	NS	0%	NS
Intermediate suspicion (62)	50.0% (31)		25.8% (8)		12.9%	
High suspicion (2)	0% (0)		0% (0)		0%	
Size (116)						
≤10 mm (17)	5.9% (1)	<.0001[b]	0% (0)	NS	0%	<.05[b]
11 to 20 cm (42)	21.4% (9)		11.1% (1)		2.4%	
21 to 30 cm (25)	28.0% (7)		0% (0)		0%	
31 to 40 cm (13)	76.9% (10)		20.0% (2)		15.4%	
≥40 mm (19)	73.7% (14)		35.7% (5)		26.3%	
Doubling rate (75)						
<1.0 (56)	37.5% (21)	<.01[a]	19.0% (4)	NS	7.1%	NS
≥1.0 (19)	73.7% (14)		21.4% (3)		15.8%	
Thyroglobulin (110)						
<1000 ng/ml (101)	28.7% (29)	<.01[a]	24.1% (7)	NS	6.9%	NS
≥1000 ng/ml (9)	77.8% (7)		0% (0)		0%	
Total (117)	35.0% (41)		12.2% (5)		4.3%	

Abbreviation: NS, not significant.
[a]Fisher's exact test.
[b]Pearson's chi-square test.

TABLE 5 Resection rates and risks of malignancy (ROM) based on four findings suggestive of malignancy[a]

Findings	Resection rate	ROM/resection	ROM/overall
0 (198)	20.2% (40/198)	5.0% (2/40)	1.0% (2/198)
1 or more (158)	74.7% (118/158)	19.5% (23/118)	14.6% (23/158)
2 or more (39)	92.3% (36/39)	33.3% (12/36)	30.8% (12/39)
3 or 4 (5)	80.0% (4/5)	50.0% (2/4)	40.0% (2/5)
4 (3)	100% (3/3)	66.7% (2/3)	66.7% (2/3)

[a]The four findings are cytological findings favouring malignancy, ultrasonography findings of high suspicion, tumour size of 30 mm or more, and tumour volume-doubling rate of 1.0/year or more.

as either 'favour benign' or 'favour malignant'.[16] However, the cytological criteria were not presented. Subsequently, several characteristics favouring follicular carcinoma have been described, including an extremely cellular appearance, numerous single cells, very little colloid, markedly distorted microfollicles, large pleomorphic nuclei, abnormal chromatin, prominent nucleoli, and mitotic activity.[17] In 2013, the Japan Thyroid Association proposed the subclassification of FNs into 'favour benign', 'borderline', and 'favour malignant', depending on cellular atypia, loss of cellular cohesiveness, loss of cellular polarity, and such structural abnormalities as trabecular, tubular and microfollicular growth patterns.[18] This system of subclassification was not widely accepted because it was difficult for general cytopathologists with limited experience in thyroid cytology to subclassify the FNs. In high-volume thyroid centres in Japan, on the other hand, such subclassification is routinely performed.[3,19,20] Widely invasive follicular carcinomas have a high predictive value for malignancy.[20] In this study, FN in the favour malignant category were defined as those with two or more dense follicles, trabecular pattern, three-dimensional microfollicles, hyperchromasia, and enlarged nuclei. We found overall ROMs of FN in the favour malignant category (non-oxyphilic, 41.2%, oxyphilic, 33.3%) were higher than those of FN in the favour benign (non-oxyphilic; 7.7%, oxyphilic; 0%) and borderline (non-oxyphilic, 8.2%; oxyphilic, 4.8%) categories. These results show that subclassification could be a useful parameter for determining clinical management. NIFTP accounted for 10.1% of resected cases. In Japan, most NIFTPs have been diagnosed as follicular adenoma.[5] ROMs of FN

before and after the proposition of NIFTP as a disease entity do not seem to significantly differ.

Ultrasonography features for distinguishing follicular carcinoma from follicular adenoma include nodules in nodules, tumour thrombus, tumour protrusion extending from the main tumour, spiculated margins, calcification, lack of a sonographic halo, hypoechoic appearance, and absence of cystic change.[8,9,21,22] These findings are more frequent in widely invasive follicular carcinomas than in minimally invasive ones. In this study, we found the ROMs of non-oxyphilic FN with an ultrasonography result of high suspicion were significantly higher than those with intermediate or low suspicion ($p < .0001$). Therefore, ultrasonography findings could be useful in determining the clinical management of FN, especially in widely invasive follicular carcinoma cases with unfavourable outcomes. Unfortunately, the significance of oxyphilic FN was unclear because there were insufficient cases with an ultrasonography result of high suspicion.

Follicular carcinomas tend to be larger than follicular adenomas.[22,23] This tendency was also observed in the present study. Boonrod et al. reported that follicular carcinomas were larger than follicular adenomas in size, with a cutoff of 40 mm.[23] Based on our results, however, the optimal cutoff value was 30 mm.

Increasing tumour volume has also been reported to increase the risk of malignancy in FN.[18] Doubling time refers to the time taken for the tumour volume to double and is commonly used to assess tumour enlargement. Doubling time is inversely proportional to the doubling rate.[6,11] A doubling rate of 1.0/year means that the tumour doubles in size in one year, and a doubling rate of 1.0 /year or higher is considered a rapidly growing tumour. We used TVDR as a measure of tumour enlargement during follow up. The calculation of TVDR is complex, but the calculator is available free of charge from the Kuma Hospital website.[6,11] The overall ROM of non-oxyphilic FNs with rapid growth (28.6%) was significantly higher than that of those with slower growth (9.9%) ($p < .05$). Given these results, TVDR could be used in determining follicular carcinoma.

Based on our results, four parameters suggestive of follicular carcinoma are cytological findings favouring malignancy, ultrasonography findings of high suspicion, tumour size of 30 mm or more, and a doubling rate of 1.0/year or more. The overall ROM of FN with one or more of the four findings was 14.6%, whereas that of FN without any of these findings was 1%. The latter is considered low-risk, and we recommend clinical management by follow up without a need for molecular testing or resection. Thus, surgical resection can be avoided in 55.6% of FN cases. We believe that this approach can serve as a reference for many institutions where molecular testing is not available, and can save costs in institutions where it is available. However, there are some barriers to the wide acceptance of our approach. Upon the adoption of active surveillance for low-risk papillary microcarcinoma, Jensen et al. stated that the strategies should focus on physicians' attitudes, patient expectations, data supporting surveillance outcomes, and promoting societal-level acceptance of surveillance.[24] We hope that all those involved in thyroid practice will recognise and accept our results and proposal. Although this approach is appropriate for low-risk FN, it is imperative that FN with metastatic lesions is unequivocally resected.

5 | CONCLUSION

We propose that FNs with no cytological findings favouring malignancy, no ultrasonography findings of high suspicion, tumour size <30 mm and TVDR <1.0/year, are considered low risk and can be followed up without the need for molecular testing.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Mitsuyoshi Hirokawa and **Ayana Suzuki**: Conception or design of the work, drafting the article, and final approval of the version to be published. **Makoto Kawakami** and **Takumi Kudo**: Data collection, data analysis, and interpretation. **Akira Miyauchi**: Critical revision of the article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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