RESEARCH COMMUNICATION

Triple Negative Status is a Poor Prognostic Indicator in Chinese Women with Breast Cancer: a Ten Year Review

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Abstract

Background: Ethnic variation in tumor characteristics and clinical presentation of breast cancer is increasingly being emphasized. We studied the tumor characteristics and factors which may influence the presentation and prognosis of triple negative breast cancers (TNC) in a cohort of Chinese women. Methods: A prospective cohort of 1800 Chinese women with breast cancer was recruited in a tertiary referral unit in Hong Kong between 1995 and 2006 and was followed up with a median duration of 7.2 years. Of the total, 216 (12.0%) had TNC and 1584 (88.0%) had non-TNC. Their clinicopathological variables, epidemiological variables and clinical outcomes were evaluated. Results: Patients with TNC had similar age of presentation as those with non-TNC, while presenting at earlier stages (82.4% were stage 1-2, compared to 78.4% in non-TNC, p=0.035). They were likely to be associated with grade 3 cancer (Hazard Ratio(HR)=5.8, p<0.001). TNC showed higher chance of visceral relapse (HR=2.69, p<0.001), liver metastasis (HR=1.7, p=0.003) and brain metastasis (HR=1.8, p=0.003). Compared with non-TNC group, TNC had similar 10-year disease-free survival (82% vs 84%, p=0.148), overall survival (78% vs 79%, p=0.238) and breast cancer-specific mortality (18% vs 16%, p=0.095). However, TNC showed poorer 10-year stage 3 and 4 specific survival (stage 3: 53% vs. 67%, p=0.010; stage 4: 0% vs. 40%, p = 0.035). Conclusions: Chinese women with triple negative breast cancer do not have less aggressive biological behavior compared to the West and presentation at a later stage results in worse prognosis compared with those with non triple negative breast cancer.

Keywords: Breast neoplasms - asian continental ancestry group - epidemiology - prognosis - mortality

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Introduction

Breast cancer is the most common cancer in women worldwide. It encompasses heterogeneous disease entities that behave differently in terms of biological aggressiveness. Traditionally, breast cancers are classified into different subtypes based on the expression of estrogen receptor (ER), progesterone receptor (PgR) and oncogene ErbB-2/human epidermal growth factor receptor 2 (HER-2). With the advancement of gene expression analysis, it was proposed that breast cancer should be classified into 5 distinct molecular subgroups: Luminal A, luminal B, HER-2-like, basal-like, and normal-like breast cancer. Proper stratification of disease according to biological and molecular markers is essential for optimal treatment.

Triple negative breast cancer (TNC) is characterized by the lack of expression of ER, PgR and HER-2 receptors. It has once been used interchangeably with basal-like breast cancer because they share similar characteristics. However, they do not belong to the same entity. Since gene expression analysis is not widely used clinically, the term "TNC" is used in most epidemiological studies. TNC draws particular attention because of its insensitivity to hormonal manipulation and target therapy, making chemotherapy the sole adjuvant treatment for this subgroup of breast cancer. The emergence of novel agents (poly-ADP-ribose-polymerase-1 inhibitor) may improve the prognosis of TNC but it is still at the very preliminary stage of research. Apart from lack of effective treatment, TNC has been reported to associate with higher grade cancers (Gluz et al., 2009) and worse prognosis.

Ethnic variations in the prevalence and prognosis of TNC are being emphasized recently. TNC has the highest prevalence in premenopausal African-American women (39%) (Carey et al., 2006), and lowest prevalence in Japanese women (8%) (Kurebayashi et al., 2007). Majority of previous studies on TNC were conducted in western cohorts and only a few examine TNC in Chinese population (Lin et al., 2009a, b; Yin et al., 2009). Yin and colleagues (Yin et al., 2009) suggested that the biological behavior and clinical outcome for TNC in Chinese patients may be more favorable than those in Western populations. On the other hand, population-based study from Korea (Lee et al., 2010) commented that it was too early to

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conclude that clinicopathological features in Asians were unique. In view of paucity of data in Chinese and Asians, we carried out a cohort study on Hong Kong Chinese women with TNC patients.

Materials and Methods

Patients

A retrospective review was performed in a prospectively collected database of breast cancer patients treated in the Breast Surgery Division, Department of Surgery, Queen Mary (QMH) and Tung Wah (TWH) Hospital, the University of Hong Kong. Public hospitals are organized into seven hospital clusters according to their locations in Hong Kong and managed by the Hospital Authority (HA) of the government of Hong Kong. QMH is the leading hospital of the Hong Kong West cluster and with TWH, its sister hospital, treat approximately 200 breast cancer patients a year not only from its catchment area but also receive referrals from other regional hospitals being a tertiary referral centre of Hong Kong. Between January 1, 1995 and December 31, 2006, a total of 1800 eligible Chinese women were included in the database. Exclusion criteria included non-Chinese, male gender, incomplete clinical records, ductal carcinoma in situ, and unknown HER2 status.

Clinicopathological, epidemiological variables and clinical outcomes were prospectively recorded and were retrospectively reviewed. Preoperatively, detailed epidemiological information (age, menstrual and pregnancy history, family history) and clinical information (mode of presentation, signs and symptoms, image abnormalities, pathological diagnosis) were documented in patients' medical records. Neoadjuvant treatment and surgical treatment were given according to international guidelines. Postoperatively, adjuvant treatment was offered according to breast cancer prognostic markers (tumor size, tumor grade, nodal status, estrogen receptors (ER) status, progesterone receptors (PgR) status, c-erb B2 score, and lymphovascular permeation) and tumor staging. Histological tumor grading was performed according to the Bloom and Richardson classification system (Bloom & Richardson, 1957). Tumor was staged according to American Joint Committee on Cancer (AJCC) criteria 6th edition (Fleming, 2001).

Patients were followed up according to standardized protocol-- every 3 months in the first two years, half yearly in the third to fifth years, annually thereafter. Tumor markers CEA and CA 15.3 were checked at each follow up session. Surveillance mammograms and ultrasound was performed every year. Investigations for metastasis such as CT scan of thorax/abdomen and bone scan or PET- CT scan were performed if recurrence or metastasis were suspected. Breast cancer remission or recurrence information was confirmed by a combination of physical examination findings, tumor markers level, surveillance mammogram and ultrasound breasts, in addition to the choice of relevant metastatic investigations performed.

The hormone receptor (HR) and HER2 receptor status, C-erb B2 score was calculated according to DAKO scoring system. Score 0 to 1+ were considered as negative for HER2 status, while 3+ was considered as positive. For c-erb B2 score 2+, whenever, possible, additional fluorescence in situ hybridization (FISH) for c-erb B2 gene amplification was performed. HER2 status was categorized according to FISH test result.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 16.0 (IBM Corp, Somers, NY) was used for all statistical analysis. The clinicopathological data between the triple negative cancer group and non-triple negative cancer group were compared by Pearson's Chi-square test or Student's t-test where appropriate. Disease free survival was defined as the time from surgery to the earliest occurrence of relapse (locoregional or distant) or death from any cause. Those without any evidence of relapse were censored at the last date they were known

Table 1. Differences of Demographic Characteristics between the Triple Negative Breast Cancer and Non-Triple Negative Breast Cancer

Demographic characteristics	Triple negative breast cancer (N=216)	Non triple negative breast cancer (N=1584)	p-value
A. Age at presentation			0.808[a]
Mean±SD	52.0±13.7	51.8±13.0	
B. Age at menarche			0.113[b]
<12	16 (12.4%)	78 (8.2%)	
≥ 12	113 (87.6%)	872 (91.8%)	
Unknown	87	634	
C. Age at menopause			0.376[b]
<50	59 (50.4%)	380 (54.8%)	
350	58 (49.6%)	313 (45.2%)	
Unknown	99	893	
D. Age at first live birth			0.321[b]
<35	116 (95.1%)	765 (92.6%)	
≥35	6 (4.9%)	61 (7.4%)	
Unknown	94	758	
E. Parity			0.024[b]
≤2	106 (62.4%)	838 (70.8%)	
>2	64 (37.6%)	345 (29.2%)	
Unknown	46	401	
F. Body mass indexc			0.774[b]
Underweight	6 (7.0%)	59 (9.3%)	
Normal weight	40 (46.5%)	271 (42.7%)	
Overweight	17 (19.8%)	145 (22.9%)	
Obese	23 (26.7%)	159 (25.1%)	
Unknown	130	950	
G. Breast feeding (years)			0.068[b]
<1	66 (78.6%)	482 (84.0%)	
1	10 (11.9%)	58 (10.0%)	
2	1 (1.2%)	17 (3.0%)	
≥3	7 (8.3%)	17 (3.0%)	
Unknown	132	1010	
H. Oral contraception			0.351[b]
Yes	48 (35.3%)	300 (31.3%)	
No	88 (64.7%)	658 (68.7%)	
Unknown	80	626	

[a]Student's t-test; [b]Pearson's Chi-square test; [c]BMI (Asian Standrads) were used according to the WHO/IASO/IOTF. The Asia-Pacific perspective: redefining obesity and its treatment. Health communication Australia Pty Ltd; 2000. Where BMI below 18.5 is underweight; from 18.5-22.9 is normal; from 23-24.9 is overweight; from 25-34.9 is obese

Table 2. Differences of Tumor Characteristics between the Triple Negative Breast Cancer and Non-Triple Negative Breast Cancer

Tumor characteristics	Triple negative breast cancer (N=216)	Non triple negative breast cancer (N=1584)	p-value[a]
AA. T stage			0.012
T1	90 (43.1%)	802 (53.5%)	
T2	106 (50.7%)	583 (38.9%)	
T3	9 (4.3%)	70 (4.7%)	
T4	4 (1.9%)	44 (2.9%)	
Unknown	7	85	
B. N stage			0.29
N0	137 (63.7%)	894 (57.9%)	
N1	49 (22.8%)	368 (23.8%)	
N2	17 (7.9%)	178 (11.5%)	
N3	12 (5.6%)	103 (6.7%)	
Unknown	1	41	
C. M Stage		0.246	
M0	212 (98.1%)	1519 (97.8%)	
M1	4 (1.9%)	35 (2.2%)	
Unknown	0	30	
D. Overall stage		0.035	
1	64 (30.5%)	555 (36.9%)	
2	109 (51.9%)	624 (41.5%)	
3	33 (15.7%)	290 (19.3%)	
4	4 (1.9%)	36 (2.3%)	
Unknown	6	79	
E. Lymphovascular permeation			0.723
Absent	133 (65.5%)	993 (68.3%)	
Suspicious	5 (2.5%)	35 (2.4%)	
Present	65 (32.0%)	426 (29.5%)	
Unknown	13	130	
F. Histological grade			<0.001
1	5 (2.5%)	297 (21.9%)	
2	47 (23.6%)	651 (48.1%)	
3	147 (73.9%)	406 (30.0%)	
Unknown	17	230	

[a]Chi-square analysis

Table 3. Relapse Rate between the Triple Negative Breast Cancer and Non-Triple Negative Breast Cancer

Relapse characteristics	Triple negative breast cancer (N=216)	Non triple negative breast cancer (N=1584)	p-value[a]
A. Relapse			0.07
Yes	19 (8.8%)	90 (5.7%)	
No	197 (91.2%)	1494 (94.3%)	
B. Bone relapse			0.092
Yes	16 (7.4%)	137 (8.6%)	
No	200 (92.6%)	1447 (91.4%)	
C. Visceral relapse			0.049
Yes	52 (24.1%)	259 (16.4%)	
No	164 (75.9%)	1325 (83.6%)	
I. Liver metastasis		0.021	
Yes	8 (3.7%)	98 (6.2%)	
No	208 (96.3%)	1486 (93.8%)	
II. Lung metastasis		0.255	
Yes	33 (15.3%)	123 (7.8%)	
No	183 (84.7%)	1461 (92.2%)	
III. Brain metastasis			0.045
Yes	11 (5.1%)	38 (2.4%)	
No	205 (94.9%)	1546 (97.6%)	

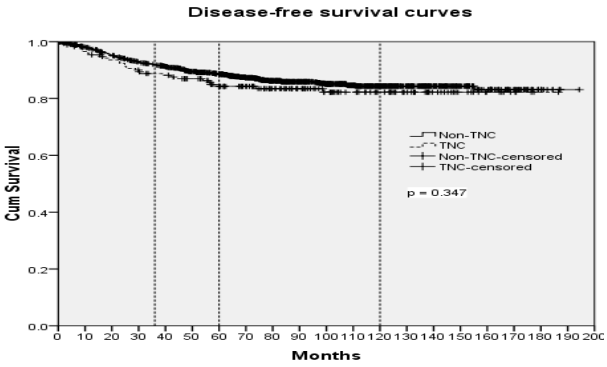

Figure 1. Disease Free Survival Curves between Triple Negative Breast Cancer and Non-Triple Negative Breast Cancer

to be alive. Overall survival was defined as the time from diagnosis to death from any cause. Survival distributions were estimated by the Kaplan-Meier product-limit method and were compared using the log-rank test. 3-year, 5-year and 10-year disease free survival and overall survival were compared. Cox proportional hazard regressions were applied to modeling the relationship between subgroups and disease-specific survival, adjusted by age at presentation, to obtain the hazard ratios (HR) and their respective 95% confidence intervals. Breast cancer-specific mortality was calculated. A two-sided p value ≤ 0.05 was considered statistically significant.

Results

In the whole cohort of 1800 women, 216 (12.0%) had TNC while 1584 (88.0%) had non-TNC. The median follow up duration was 7.2 years. The baseline characteristics of patients with triple negative breast cancer and patients with non-triple negative breast cancer are presented in Table 1.Patients with TNC had similar age of presentation as those with non-TNC, more of them were multiparous. Other demographic characteristics were similar between the two groups. Table 2 described the tumor characteristics of the two cancer groups. TNC presented at earlier stages (82.4% were stage 1-2, compared to 78.4% in non-TNC, p=0.035).They were likely to be associated with grade 3 cancer [Hazard Ratio (HR) =5.8, 95% Confidence interval (CI) 3.0-11.4, p<0.001). The lymphovascular permeation did not differ between the groups.

As shown in Table 3, TNC showed higher chance of visceral relapse HR=2.69 (95% CI 1.56-4.65, p<0.001)], liver metastasis [HR=1.7 (95% CI 1.2-2.4, p=0.003] and brain metastasis [HR=1.8 (95% CI 1.2-2.6, p=0.003)]. There was no significant difference in rate of local relapse and bone metastases between the two groups.

Higher proportion of TNC patients (77.3%) received chemotherapy than non-TNC patients (49.6%) (Table 4).Both groups were matched in terms of sequence or regime of chemotherapy. Similar proportion of both groups received radiotherapy.

14.8% (N=32) TNC patients died from cancer, compared to 11.0% (N=174) in non-TNC group. 2.8% (N=6) TNC patients and 3.3% (N=52) in non-TNC group died from other causes although these difference were not clinically significant (p= 0.34). Of those who survived,

Table 4. Regime of Chemotherapy Received between the Triple Negative Breast Cancer and Non-Triple Negative Breast Cancer

Treatment regime	Neoadjuvant chemotherapy			Adjuvant chemotherapy		
	TN (N=28)	Non-TN (N=153)	p-value[a]	TN (N=147)	Non-TN (N=605)	p-value[a]
CMF[b]	1 (3.6)	1 (0.7)	0.75	60 (40.8)	208 (34.4)	0.594
FEC[b]	16 (57.2)	84 (54.9)		31 (21.1)	127 (21.0)	
FAC[b]	2 (7.1)	7 (4.5)		14 (9.5)	82 (13.6)	
AC[b]	2 (7.1)	10 (6.5)		17 (11.6)	61 (10.1)	
FEC+T[b]	1 (3.6)	19 (12.4)		0 (0.0)	0 (0.0)	
TCH[b]	0 (0.0)	1 (0.7)		0 (0.0)	6 (1.0)	
Others/No	6 (21.4)	31 (20.3)		25 (17.0)	121 (19.9)	

[a]Chi-square analysis; [b]CMF, Cyclophosphamide, methotrexate and fluorouracil; FEC, Fluorouracil, Epirubicin and Cyclophosphamide; FAC, Fluorouracil, Adriamycin and Cyclophosphamide; AC, Adriamycin and Cyclophosphamide; FEC + T, Fluorouracil, Epirubicin, Cyclophosphamide and Taxane; TCH, Taxotere, Carboplatin and Herceptin

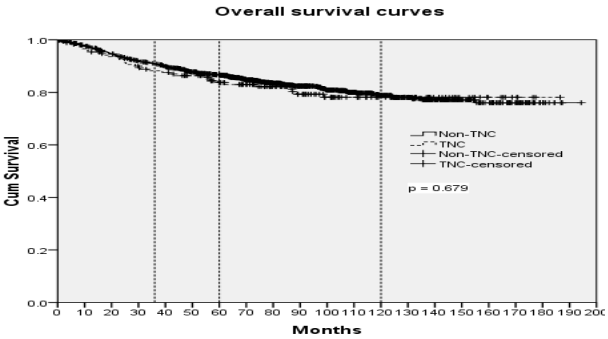

Figure 2. Overall Survival Curves between Triple Negative Breast Cancer and Non-Triple Negative Breast Cancer

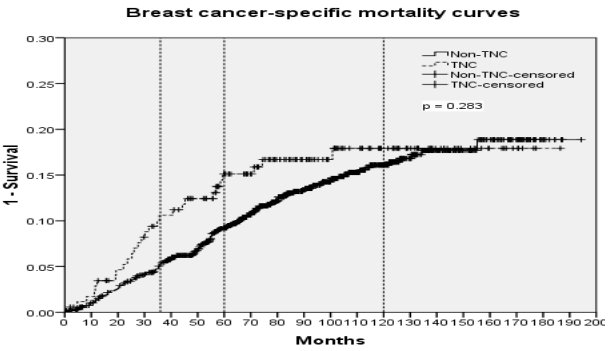

Figure 3. Breast Cancer-Specific Mortality Curves between TNC and Non-TNC Patients

4.6% (N=10) TNC patients had recurrence, compared to 6.9% (N=110) in non-TNC group The disease-free survival at 3-year, 5-year and 10-year of TNC and non-TNC patients were 89% and 92% (p=0.577), 84% and 89% (p=0.535), and 82% and 84% (p=0.148) respectively (Figure 1). The overall survival (Figure 2) at 3-year, 5-year and 10-year of TNC and non-TNC patients were 88% and 91% (p=0.710), 83% and 87% (p=0.991), and 78% and 79% (p=0.238) respectively. The mean time to death was 7.9±0.3 years and 8.3±0.1 years in TNC and non-TNC patients at their 10th year of censoring respectively (p=0.238). When the survival were adjusted for the stage of breast cancer diagnosis (Figure 3), TNC patients had poorer 10-year stage 3 and 4 specific survivals compared with the non-TNC group (stage 3: 53% vs. 67%, p=0.010; stage 4: 0% vs. 40%, p = 0.035).

The breast cancer-specific mortality rates at 3-year, 5-year and 10-year of TNC and non-TNC patients were 11% and 5% (p = 0.403), 16% and 9% (p = 0.652), and 18% and 16% (p = 0.095) respectively.

Discussion

The prevalence of TNC in several large unselected breast cancer patient cohorts is around 17% (Cheang et al, 2008; Rakha et al, 2007). In high risk ethnic group like African-American women, TNC can be as high as 39% (Carey et al., 2006). In our cohort, the prevalence of TNC is around 12%, which was similar to that previously reported (Yin et al., 2009). Although the risk factors for hormonal responsive breast cancer were well defined, the risk factors for triple negative breast cancer showed inconsistent results in different studies. We found there was no difference in age of presentation in TNC and non-TNC group in Hong Kong Chinese women, whereas TNC presented at a statistically younger age in the West. Of note is the overall age of presentation in our cohort is young compared to that of the West which may be the reason why no difference is seen between the two groups (Bauer et al., 2007). Higher parity was reported to be associated with TNC (Millikan et al., 2008; Kwan et al., 2009), which was congruent with our analysis. In the literature, obesity and lack of breast-feeding were associated with TNC (Kwan et al., 2009) but this could not be demonstrated in our study. This is probably due to the significant missing data in our database regarding with the recording of these parameters. Moreover with obesity, we have also adopted the use of the BMI range adjusted for use on Asian Standards due to the different degree of obesity seen in Asian countries compared to the West (Table 1) and hence direct comparison may be difficult. The role of sex hormone estrogen and progesterone in the development of TNC is largely unknown, since by definition TNC is unresponsive to these sex hormones, hence, factors which affect hormone levels such as parity, breast feeding and obesity may play a role in increasing or decreasing the risk of having hormonal responsive cancer, rather than on TNC itself.

In conclusion, there were similarities and differences in prevalence, risk factors, clinicopathological factors, recurrence risk, and survival result of triple negative cancer compared to the West. Chinese women with triple negative breast cancer did not have less aggressive biological behavior. Larger-scale study on different

ethnicities will increase our understanding in TNC to achieve more personalized management.

Concurring with findings from the Nottingham Tenovus Primary Breast Carcinoma Series (Rakha et al., 2007) , TNC in our cohort was more likely to be associated with high tumor grade. On the contrary, we observed that TNC patients presented at earlier stages despite the presence of higher grade tumors in the TNC group. Presence of lymphovascular invasion, is a suggested prognostic indictor. However, we did not observe any difference between the two groups.

Several studies have reported conflicting results of locoregional recurrences in TNC. Haffty et al. (2006) and Tan et al. (2008) found no association of triple negative cancer with shorter local relapse-free survival, which is similar to our findings in our cohort. On the other hand, Rodriguez-Pinilla et al reported that triple negative breast cancer had a higher percentage of local recurrence (Rodriguez-Pinilla et al, 2006). Dent et al. (2009) also concluded that concluded that triple negative breast cancer were four times more likely to experience a visceral metastasis within five years of diagnosis than those with other types of cancer. In our cohort, TNC was also found to have a worse outcome and was 2.69 times more likely to experience visceral relapse. Patients with TNC in our study also had 1.8 times more risk of developing brain metastasis. It had been reported that TNC patients had shorter survival after diagnosing brain metastasis when compared to non TNC counterparts and hence is a poor prognostic indicator (Saip et al., 2009). Consistent with findings reported in Western population (Rodriguez-Pinilla et al., 2006; Dent et al., 2009), we did not find any difference between the TNC and non TNC groups in incidence of bone metastasis.

Majority of studies in the West showed worse prognosis for TNC group within 3-5 years (Tischkowitz et al., 2007; Dent et al., 2009), and some suggested the differences between TNC and non-TNC regarding overall survival wear off at 10 years of follow-up (Tischkowitz et al., 2007). In this aspect, we observed a similar breast cancer-specific mortality rate, disease-free survival and overall survival between groups. The TNC patients' prognosis may be partly improved by increase utilization of chemotherapy (77.3%), compared to 49.6% in non TNC patients. When the patients were stratified by stage, TNC patients with stage 3 or 4 had significantly poorer survival at 10 years; this of which has not been reported previously in other studies. We postulate that it is likely that prognosis of early breast cancer is so good in modern era and the differences between these groups would need alarger sample size and longer follow up to demonstrate. While for the advanced breast cancer with high event rate, triple negative subtype definitely has a poorer prognostic impact on the survival. Our findings suggests that Chinese TNC cohort has the same (if not worse) biological aggressiveness compared to the West, which is in contrary to a previous study on Chinese patients with TNC by Yin et al. (2009). The differences between various Chinese cohorts itself may be explained by the environmental and lifestyle factors. Due to the ruling under the British government fo 99 years, Hong Kong Chinese cohort generally have more Westernized lifestyle and had higher socioeconomic status compared with the mainland Chinese cohort which has only recently been exposed to more Western influence. There may also be different genetic-environmental influences which may contribute to the diversity of TNC presentation and prognosis between different Chinese cohorts. Follow up longer term research studies in Mainland China may reveal differences as the lifestyle of Mainland Chinese are increasingly exposed to Western influence.

The strengths of our study are firstly, the comprehensive prospectively collected database and life-long follow-up data which can be obtained. All phases of treatments were performed at a tertiary cancer center, with good quality of care of international standards and consistency in diagnosis and treatment. On the other hand, some of our results should be interpreted with caution due to the underreporting of some data, in particular, risk factors particularly in those data collected during early years of this period of analysis.

In conclusion, there were similarities and differences in prevalence, risk factors, clinicopathological factors, recurrence risk, and survival result of triple negative cancer compared to the West. Chinese women with triple negative breast cancer did not have less aggressive biological behavior. Larger-scale study on different ethnicities will increase our understanding in TNC to achieve more personalized management.

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The author(s) declare that they have no competing interests.

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