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A Study on Human Papillomavirus on Human Papillomavirus Genotype and Cervical Cancer, Case Study a University Community in Wuhan

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ABSTRACT

Cervical cancer is a common female malignant tumor. According to the 2018 statistics in China, the rate shows an increasing trend and is currently at 7.5/100.000. As a developing country, the statistical data does not cover all areas in China, and there is no specific data targeting university communities about cervical cancer. The exampled university community owns a relatively stable and civilized faculty, which could represent the current status of cervical cancer in this area. Based on the HPV-related cervical cancer screening conducted during community medical examinations at a university at Wuhan, this paper studies the distribution and trend of positive cytology (TCT), human papilloma virus comes infection and genotype, analyzes the cervical cancer pathogenesis regularity in university communities, and explores the relationship between cervical cancer and the characteristics and genotype of Human papillomavirus (HPV) infection in the university communities, which provides the theoretical basis of HPV vaccine immunization. This research shows that among the 5038 TCT examinees, 4995 (99.1%) were NILM and 43 (0.9%) were abnormal in TCT, among which 30 (0.6%) were ASCUS. LSIL was detected in 13 cases (0.3%), and no other cytological abnormalities were found. According to the analysis of 10% of the population in different age groups, TCT abnormalities were most common in the age groups of 21-33 and 47-49 in the community of our university, accounting for 16.3% of the total number of abnormal people. The age groups of 44-46 and 50-52 years old account for 14.0% of the total abnormal population. The change of bacterial community and bacterial vaginosis were the main causes of microbial infection, accounting for 8.0% of the total abnormalities. Next was fungal infection, accounting for 4.0% of the total abnormalities. Trichomonas and actinomycetes are relatively rare. The morphological changes were mainly atrophic changes of epithelial cells, without inflammation, accounting for 77.1% of the total abnormalities. Secondly, the number of inflammatory reaction and inflammation associated with atrophy of epithelial cells was approximately the same, accounting for 3.5% and 3.6% of the total abnormalities, respectively. The age group of 64-71 years old is the main age group for the atrophy of epithelial cells with inflammation, accounting for 42.9% (12/28) of the total number of people with atrophy of epithelial cells with inflammation. With a co-analysis of TAT and HPV for 2756 samples, we've found that HPV genotypes and TCT results are positively correlated with the detection rate of cervical cancer, which means Joint detection is helpful to improving the detection rate. After a statistically analyzed by artificial neural network (ANN) to above data, it has suggested that HPV-39, HPV-5, HPV-16 and HPV-52 are the four major factors causing cervical epithelial cell mutation in this university community. This study compares the main cancer ogenic HPV sub genotypes in the exampled university community and immune subtypes provided by current HPV vaccines, suggesting to Inject vaccines containing HPV-16、HPV-52、HPV-58、HPV-51、HPV-39 and HPV-5 subtype in this community.

Keywords: *cervical cancer Human papilloma virus University community HPV Genotyping Artificial neural network*

INTRODUCTION

Both epidemiology and basic research have confirmed that from the persistent infection of HPV [10] cervical epithelial cells to cervical precancerous lesions, further development to CIN, and finally to cervical cancer, is a long-term process of qualitative change to quantitative change. It takes about 8-15 years [11].

This long-term evolution provides an excellent opportunity for early detection, early diagnosis and treatment of cervical lesions, early detection and early treatment of cervical lesions, and reduction of cervical cancer. Incidence plays a crucial role. There are limitations in the method of single cervical cytology or single detection of HPV gene subtypes. Cervical cytology TCT test can only indicate the presence or absence of cervical malignant lesions, suggesting the extent of abnormal cell morphology, but cannot determine the cause (such as HPV infection). The HPV test only indicates the possibility of cervical cancer, but it is not certain whether cervical lesions or cervical lesions have developed. In this study, a comprehensive analysis of the results of 2778 TCT and HPV subtypes was conducted to analyze the effects of cytological TCT and HPV subtypes on early diagnosis of cervical cancer, and the complementarity of the two screening methods was explored.

Research Objects

This study is mainly aimed at faculty and staff members who have lived in the community for a long time and their families. Excluding the group of students with greater mobility, the research object is relatively fixed, which can reflect the true state of cervical cancer infection in this community. Specimen source: Select faculty members and their families who have come to the community hospital for gynecological examination from January 2016 to December 2017 as the research object information, and record detailed information, including name, work unit, occupation, telephone , history of marriage and childbirth, past health status (including gynecological surgery history, etc.). A total of 5,038 samples of medical examiners were collected. Participants are 21 years old and 90 years old. The cervical cancer screening statistics were approved by the hospital ethics committee.

Research Methods

The data was analyzed using Artificial Neural Networks (ANN) using IBM's SPSS 20.0 software. P < 0.05 was considered as a significant difference and was statistically significant.

Results

Combined Screening and Analysis of Cervical Cytology and HPV Gene Subtypes

Among the 2756 subjects who participated in the combined screening of cervical cytology and HPV subtypes, 228 were HPV-positive, with an average positive rate of 8.3%. Among the populations with TCT cytology results of NILM, the positive rate of HPV detection was7.7% (211/2730), the positive rate of HPV detection was 46.7% (7/15) in the population with TCT cytology results of ASCUS, and the positive rate of HPV detection was as high as in the population with TCT cytology results of LSIL. 90.9% (10/11). See Table 3-1.

Table3.1. *Test Results of TCT and HPV in Different Populations in Colleges and Universities*

TCT results	Number of cases	HPV Negative		HPV Positive%
NILM	2730	2519	211	7.7
ASCUS	15	8	7	46.7
LSIL	11	1	10	90.9
Total	2756	2528	228	8.3

In the community of 2756 people with TCT results of NILM, 7.7% of them still detected HPV positive, that is, there was human papillomavirus infection, indicating a single detection of TCT, there is a certain amount of missed diagnosis rate; and the TCT result is ASCUS In the population, that is, in the population with cytological findings of atypical squamous epithelial cells, 46.7% of them detected HPV positive, indicating that cytological changes are not only caused by HPV infection, but there may be other factors that can cause Cytological changes, if only HPV genotyping is selected, there is also a certain amount of missed diagnosis. In the population with cytological results of TCT for LSIL, the positive rate of HPV detection was as high as 90.9%, and the consistency between the two was high, indicating that the detection results of HPV and TCT were positively correlated with the detection rate of cervical cancer, suggesting joint detection. Helps improve the detection rate of cervical cancer.

The chi-square test was used to analyze the negative and positive TCT cytology results and the age of the subjects. The results showed that the P value was 0.997>0.05, and there was no significant difference. The chi-square test was used to test the negative result of HPV genotyping. The positive and the age of the subject were analyzed. The P value was 0.008.0.01, which was statistically significant. Therefore, the positive data of the above human papillomavirus (HPV) genotyping (type 25) were further tested. According to the age range of the previous 10% population distribution, the comparative analysis was carried out. The positive distribution of HPV is shown in Table 3-2 below. The positive detection rate of human papillomavirus (HPV) in the 21-33 age group was 16.6% (35/211) in the population of the university community in the normal cytology of liquid-based thin-layer cytology (TCT). The positive detection rate of human papillomavirus (HPV) was 13.3% (28/211) in the 44-46 age group; then 39-43 years old, 53-56 years old, 47-49 years old and 50-52 years old. In these four age ranges, the positive detection rate of human papillomavirus (HPV) was10.9% (23/211), 10.9% (23/211), 10.4% (22/211) and 10.4% (22/211); that is, except for the age of 21-33, the age range of 39-56 years old The incidence of human papillomavirus (HPV) infection is also high, the infection is universal, and the infection rate in the 21-33 age range is not low. Therefore, cervical screening should not only focus on people aged 45 and over as reported. Young people should also pay attention to the same high risk of HPV infection. In the population of TSC cytology test results of ASCUS, that is, the cytology test results for atypical squamous epithelial cells, there is universality and no obvious age distribution characteristics. In the university community, the positive cytology of TCT is LSIL, that is, in people with low squamous intraepithelial lesions, the positive rate of HPV in both ages of 47-49 and 50-52 is 27.2%.(3/11), that is, the age range of 47-52 years old is the age group with higher risk of cervical cancer in the university community. The reason for the analysis is that the age group has a higher chance of being in menopause, which may be related to the change of endocrine status and should cause This age group pays enough attention to cervical cancer, increases missions, and strengthens cervical cancer screening for this age group.

Table3.2. *Age Distribution of HPV Positive Population in College Community*

Age range	NILM	ASCUS	LSIL
21-33	35	1	1
34-38	16	1	0
39-43	23	1	1
44-46	28	1	1
47-49	22	0	3
50-52	22	2	3
53-56	23	0	1
57-63	17	0	0
64-71	15	1	0
72-91	10	0	0
Total	**211**	**7**	**10**

Artificial Neural Network (Ann) Analysis

Using artificial neural networks for statistical analysis, ANN was used to measure the importance of the covariates to predict the impact of each HPV genotype. The working principle of ANN is to simulate the mode of transmitting information of brain neurons. It is an adaptive nonlinear dynamic system based on a large number of simple mathematical models. It is closer to the human brain in terms of its principle and function. Environment, summarizing the law. The ANN analysis system needs to learn and work again to obtain knowledge through the process of the learning phase.

Therefore, the trade-off covariate is allowed to determine the degree of influence of the importance variable on the multi-factor phenomenon. The ANN analysis system consists of three layers (one input layer, one hidden layer, one output layer) to form a feed forward analysis system. The data is randomly divided into training group (70%) and test group (30%). During the statistical analysis process, we determine the number of hidden units by the test data criteria: the "best" number of hidden units is the unit with the least error in the test data as the learning rule.

The weight of the covariate is updated each time it is updated. In addition, Kaplan-Meier method was used to estimate the incidence of cervical cell abnormalities caused by different types of HPV genotypes in the university community. In addition, the data is summarized using basic descriptive statistical methods. Using artificial neural network (ANN) analysis, 2756 populations of human papillomavirus (HPV) genotyping (type 25) and liquid-based thin-layer cytology (TCT) cytology was selected for simulation analysis. These data were randomly assigned to the training group 1942/2756 (70%) as the basic data for constructing the artificial neural network.

The model was verified with the remaining 30% (814/2756). In the artificial neural network model successfully constructed, the training group squared error sum is 20.795, the prediction error percentage is 1.1%; the test group square error sum is 6.507, and the prediction error percentage is 0.9%. The input layer selects the HPV genotype as a covariate, and the hidden layer includes the HPV genotype that is not detected in the training group as an activation function. The output layer includes 0: cervical cytology (TCT) for detecting cervical

Cell morphology (TCT-) and 1: cervical cytology (TCT) for detecting cervical cell

Table3.3. *Four Sets of Input Layers for Building an ANN Model (Random Data)*

	H (1)	H (2)	H (3)	H (4)
HPV6	0.001	0	0	0
HPV11	0.001	0	0	0
HPV16	0	0	0.227	0.091
HPV18	0.002	0	0	0
HPV31	0	0.067	0.027	0
HPV33	0.003	0	0	0.045
HPV35	0	0.067	0	0
HPV39	0	0	0.2	0.045
HPV40	0.001	0	0	0
HPV42	0.002	0	0	0
HPV43	0.001	0	0	0
HPV51	0.001	0	0.187	0.136
HPV52	0.001	0.967	0.107	0.182
HPV53	0.003	0	0.027	0
HPV56	0	0	0.173	0.091
HPV58	0	0	0.36	0.182
HPV59	0.004	0	0	0
HPV66	0.003	0	0	0.045
HPV68	0.004	0	0.013	0.045
HPV81	0.001	0.033	0.013	0
HPV83	0.001	0	0	0
Other subtypes	0.064	0.17	0.393	0.342

Using artificial neural network (ANN) technology, we observed that the random ratios obtained four sets of data (Table 3-3), and the absolute value of the H(3) ratio was the smallest in the group of normal cervical cell morphology (TCT-). , 0.854 (Table 3-4), that is, H (3) group data as the basis of artificial neural network construction, can be used to predict that those HPV genotypes will not cause abnormal cervical cells. The absolute value of H(3) ratio is the highest in the group of cervical cell morphology abnormalities (TCT+), so if you want to use H(3) composition ratio data to predict those HPV genotypes will lead to abnormal cervical cell abnormalities, The composition of the H(3) group data must be further analyzed.

Table3.4. *Output layers corresponding to Table 3-3*

	TCT−	TCT+
H (1)	0.989	0.011
H (2)	0.92	0.08
H (3)	0.854	0.146
H (4)	1.091	-0.091

The H (3) group consists of the following: The input layer contains 21 HPV genotypes: HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV. -39, HPV-40, HPV-42, HPV-43, HPV-51, HPV-52, HPV-53, HPV-56, HPV-58, HPV-59, HPV-66, HPV-68, HPV-81 , HPV-83. morphology abnormality (TCT+) as a dependent variable.

The hidden layer included four HPV genotypes that were not detected in the training group, namely HPV-26, HPV-44, HPV-45 and HPV-73. Model accuracy analysis of the model (see Figure 3-5 below):The area below the line 0 is the baseline. The area under curve 1 is the predicted HPV subtype, which results in a cervical cell morphology normal (TCT-). The accuracy of the model is 77.8%. The area under curve 2 is the prediction of HPV subtypes leading to cervical cells. The model accuracy (area under the curve) with a morphology abnormality (TCT+) was also 77.8%. Can be used to predict the risk of HPV gene subtypes leading to cervical cell abnormalities.

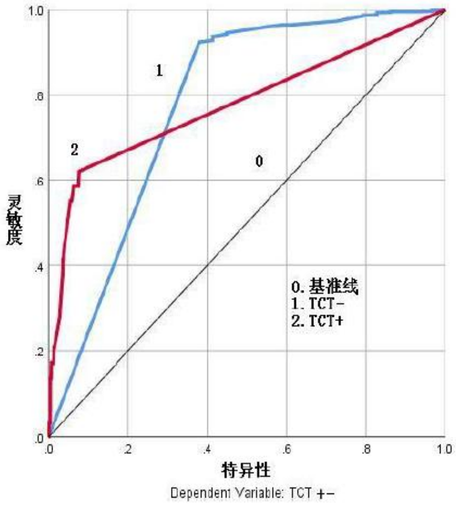

Figure3.5. *HPV Gene Subtype Prediction Accuracy Model*

Artificial neural network technology can be used to predict the risk of cervical cancer in different HPV subtypes. From Figure 3-6, we observed the most important HPV-39 predicting cervical cell dysfunction (importance: 0.73; standardization importance: 100%), and importance represents the risk of cervical cancer in the HPV subtype. Probability, the importance of standardization is based on HPV-39 and the importance relative to HPV-39); the other types are HPV-58 (importance: 0.69; standardization importance: 95.4%); HPV-16 (Importance: 0.67; Standardization Importance: 91.6%); HPV-52 (Importance: 0.63; Standardization Importance: 83%); HPV-56 (Importance: 0.55; Standardization Importance: 75.5%); HPV-53 (Importance: 0.49, Standardization Importance: 66.7%); HPV-31 (Importance: 0.48; Standardization Importance: 66.5%); HPV-81

(Importance: 0.46; Standardization Importance: 63.1%); HPV-51 (importance: 0.45; standardization importance: 61.5%); HPV-59, HPV-18, HPV-42, HPV-83, HPV-43, HPV-11, HPV-6, HPV-40, HPV-35 These 9 types are consistent (importance: 0.43; standardization importance: 59.7%); HPV-68 (importance: 0.34; standardization importance: 46.6%); HPV-66 and HPV-33 are consistent (importance: 0.31) Standardization importance: 42.7%). According to the ANN analysis, other HPV genotypes have less impact on the risk of cervical cell variability.

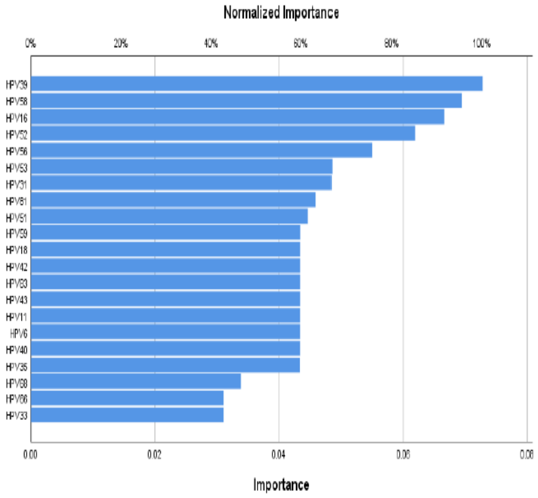

Figure3.6. *Distribution of Risk Rates for Cervical Cancer Caused By HPV Subtypes*

The Choice of Existing HPV Vaccine in the Community of this University

To analyze the current status of HPV infection in the college community, analyze the protective effects that existing HPV vaccines can provide. Inoculation of HPV vaccine to prevent HPV infection, so as to achieve the purpose of preventing cervical cancer. The current development of HPV vaccines is focused on the synthesis of virus-like particles (VLPs). VLPs are very similar in morphology to HPV but do not contain HPV viral DNA. VLP can successfully induce neutralizing antibodies against the L1 epitope, thereby protecting the same HPV subtype. The status of HPV infection in the college community: HPV-52 (21.7%), HPV-58 (16.5%), HPV-16 (10%), HPV-51 (9.6%), HPV-52 (16.5%), HPV-39 (6.9%), HPV-56 (6.6%), HPV-68 (4.8%), HPV-59 (3.7%), HPV-53 (3.5%), HPV-33 (3.1%),HPV-66 (3%), HPV-18 (1.7%), HPV-31 (1.4%), HPV-33 (1.4%); HPV-45 (0.3%), HPV-6 (0.3%), HPV- 11 (0.3%)

At present, China has approved the listing of 2%/4/9 price HPV vaccines, and now evaluates the effective protection of these vaccines in this community: For the 2-valent HPV vaccine, Cervarix, produced by GlaxoSmithKline, was launched in 2007. High-risk HPV 16 and 18 for the 2-valent vaccine can only effectively protect against HPV infection of 11.7% [HPV-16 (10%) + HPV-18 (1.7%)]. Its vaccine protection does not include the following 13 high-risk HPV subtypes: HPV-52, HPV-58, HPV-51, HPV-39, HPV-56, HPV-68, HPV-59, HPV-53, HPV-33 HPV-66, HPV-31, HPV-33; HPV-45.

For the 4-valent HPV vaccine, Gardasil was produced by Merck and was launched in 2006. Targeted high-risk HPV16 and 18 and low-risk HPV6 and 11 are also effective only 12.3% [HPV-16 (10%) + HPV-18 (1.7%) + HPV-6 (0.3%) +HPV-11 (0.3%)] HPV infection. Its vaccine protection does not include the following 13 high-risk HPV subtypes: HPV-52, HPV-58, HPV-51, HPV-39, HPV-56, HPV-68, HPV-59, HPV-53, HPV-33 HPV-66, HPV-31, HPV-33; HPV-45.

For the 9-valent HPV vaccine, Gardasil was produced by Merck and was launched in 2014. Targeted high-risk HPV16/18/31/33/45/52/58 and low-risk HPV6 and 11 can only effectively protect 55.3% [HPV-16(10%)+HPV -18 (1.7%) [HPV-31 (1.4%) + HPV-33 (3.1%) + HPV-45 (0.3%) + HPV-52 (21.7%) + HPV-58 (16.5%) + HPV-6 (0.3%) + HPV-11 (0.3%) HPV infection. Its vaccine protection does not include the following eight high-risk HPV subtypes: HPV-51, HPV-39, HPV-56, HPV-68, HPV-59, HPV-53, HPV-33, HPV-66.

DISCUSSION

The study found that among the 2756 subjects who were screened in the 2016-2017 joint screening of the university community, 7.7% of the people with cytological results of NILM were positive for HPV, ie, there was human papillomavirus infection. There was a certain amount of missed diagnosis rate in a single TCT test. In the population with ATCUS cytology, the population of ASCUS, ie, the cytology test results were atypical squamous cells, 46.7% of them detected HPV positive, indicating Cytological changes are not only caused by HPV infection, but there may be other factors that can lead to cytological changes. If only HPV genotyping is selected, there is a certain amount of missed diagnosis. In the population with cytological results of TCT for LSIL, the positive rate of HPV detection was as high as 90.9%, and the consistency between the two was high, indicating that the detection results of HPV and TCT were positively correlated with the detection rate of cervical cancer, suggesting joint detection. Helps improve the detection rate of cervical cancer. Through ANA analysis, this study found that HPV-39, HPV-58, HPV-16 and HPV-52 have a higher probability of infection of cervical epithelial cells in the community, targeting the above four Infection of HPV gene subtypes should be early detection of early intervention to avoid the occurrence and development of cervical malignant lesions. This study found that the most effective protective factor for the HPV subtype infection in the community of the university is the 9-valent HPV vaccine Gardasil produced by Merck, which is recommended for immunization

CONCLUSION

Cervical cancer, as a unique malignant tumor of women, brings profound mental pain and heavy economic burden to countless families, and brings huge economic losses to the country and society every year. Therefore, the early detection of cervical cancer has great social and economic value. Cervical cytology TCT test can only indicate the presence or absence of cervical malignant lesions, suggesting the extent of abnormal cell morphology, but can not determine the cause (such as HPV infection). The HPV test only indicates the possibility of cervical cancer, but it is not certain whether cervical lesions or cervical lesions have developed. This study found that the mode of joint screening can not only detect abnormal cell morphological changes at an early stage, but also detect HPV subtypes with high canceration tendency in time, so as to achieve early detection of early cervical cancer. This paper is based on the screening of cervical tissue cytology and molecular epidemiology in 5,038 subjects in a college community in Wuhan City. Firstly, the main pathogenic factors and screening methods for cervical cancer are comprehensively described for subsequent cervical cancer. Joint screening provides a theoretical basis. Secondly, 5038 cases of community subjects were selected as the research object. The joint screening of cervical cytology and HPV gene subtypes was carried out. The main types of HPV infection in this community were screened and the distribution characteristics of HPV genes in this community were determined. The research of this thesis shows that: 1) The main subtypes of HPV in this community are significantly different from the main subtypes of HPV in South America and Europe, especially as the main type of HPV-18 in North America and Europe, which is not common in this university community. 2) HPV-52, which is highly developed in the college community, is not seen in North America and Latin America; 3) the major subtypes of HPV vary from race to race. Compared with different regions in China (such as Shaoxing and Shandong), the genotypes of HPV-infected people detected by this community are higher than those in the top 5 HPV-52, HPV-58, HPV-16, HPV- 51, HPV-39 is not completely consistent, the top three HPV subtypes are roughly the same, indicating that the main subtypes of HPV in this community are consistent with major subtypes in most parts of the country, and are instructive for the selection of HPV vaccines. The above results can provide theoretical basis and data support for the early diagnosis and early intervention of cervical cancer in the community. This paper further analyzes the commonality and complementarity of cervical cytology and HPV subtype screening by means of joint screening, suggesting that combined detection can improve the detection rate of cervical cancer. At the same time, through ANA analysis, it was found that the HPV-39, HPV-58, HPV-16 and HPV-52 infections of this community had a higher probability of infection of cervical epithelial cells. This study has important social and economic benefits in reducing the incidence of cervical cancer. Cervical cytology and combined screening of HPV subtypes can significantly improve the detection rate of cervical cancer, which can be used as a basis for early diagnosis and early treatment of patients, and provide a basis for the selection of effective vaccine types.

RECOMMENDATIONS

This study is the first to conduct a statistical analysis of cervical cancer screening in colleges and universities. Screening revealed differences in regional distribution of HPV subtypes, and models of human papillomavirus HPV infection by artificial neural network (ANN) model. Correlation of abnormal changes in cervical cytology was assessed, and multiple genotypic cross-over analyses were performed at appropriate times to assess whether different types of human papillomavirus HPV could have a similar risk of affecting cervical lesions. The following four HPV subtypes (HPV-39, HPV-58, HPV-16, and HPV-52) were found to have a high incidence of abnormal lesions in cervical epithelial cells. The methods and conclusions of this study need to be improved in the following three aspects.

- In this study, only one community was selected. These results need to be further verified in a broader scope. I hope that multiple community samples can be added for joint analysis next time.
- This study only counts the current subjects, and does not conduct long-term follow-up investigations on patients with abnormal lesions. The next step is to conduct statistical analysis of follow-up information.
- The current existing commercialized HPV vaccine does not effectively protect the major HPV gene subtypes of the community population, and hopes to provide data for the development of HPV vaccines for the local population as a theoretical basis. It is also recommended to develop new vaccines for the highly carcinogenic HPV-51 and HPV-39 in this community.

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