The Changing Characteristics of Intestinal Flora in Hypertensive Patients with Different Cardiovascular Risk Stratification on the Basis of 16S rRNA Technology

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Introduction. This study aims to reveal the changes in gut microbiota in hypertensive patients with different cardiovascular risk stratification and to provide a new perspective for the prevention and treatment of hypertension. Hypertension, as a common cardiovascular disease, is receiving increasing attention for its harm. There are differences in the severity and prognosis of hypertension patients with different cardiovascular risk stratification. The gut microbiota, as an important component of the human microbiota, is closely related to the occurrence and development of various diseases. Previous studies have shown a potential association between dysbiosis of gut microbiota and hypertension. For example, the blood pressure levels of rats with primary hypertension are correlated with changes in gut microbiota, with an increase in fecal variability and a significant decrease in the production of esters and butyric acid bacteria. Sequencing analysis of gut microbiota in a small cohort of human hypertensive patients also revealed dysbiosis, reduced richness and diversity of gut microbiota. However, the specific changing characteristics of in gut microbiota in hypertensive patients with different cardiovascular risk stratification are currently unclear. This study will conduct in-depth analysis of gut microbiota in hypertensive patients with different cardiovascular risk stratification, including low-risk, moderate risk, high-risk, and extremely high-risk, based on 16SrRNA technology. By comparing the differences in the types, quantities, distribution, and metabolites of gut microbiota among patients in different stratification groups, potential patterns and characteristics can be explored. This study is expected to provide new basis and ideas for a deeper understanding of the pathogenesis of hypertension, optimizing treatment strategies, and preventing cardiovascular complications, and has important clinical significance and application value.

Keywords. 16s rRNA Technology, Cardiovascular System, Stratified Hypertension, Gut Microbiota, Changing Characteristics

INTRODUCTION

As an advanced molecular biology technology, 16S rRNA technology has high sensitivity and specificity, and can accurately detect the composition and changes of

intestinal flora. Cardiovascular risk stratification is an important criterion for assessing the severity and prognosis of hypertensive patients, including low-risk, moderate-risk, high-risk and very high-risk levels. Hypertension, as a common chronic disease, poses a huge threat to patients' health. The intestinal flora is a complex microbial community. And changes in its structure and function are closely related to the occurrence and development of hypertension. Using 16S rRNA technology to explore the changing characteristics of the intestinal flora in hypertensive patients with different cardiovascular risk stratifications will help to gain a deeper understanding of the pathogenesis of hypertension.

In low-risk patients, the intestinal flora may be relatively stable, and the proportion of certain beneficial bacteria may be high. In high-risk patients, the flora diversity may decrease, and the number or proportion of harmful bacteria may increase. In-depth research on these changing characteristics can not only provide new targets for the precise treatment of hypertension, but also provide important theoretical support for preventing the deterioration of cardiovascular disease. At the same time, it also opens up new avenues for the development of targeted probiotic preparations or dietary intervention strategies.

1 MATERIALS AND METHODS

1.1 Objectives

A total of 85 patients with essential hypertension were included in this study. All the participants were diagnosed with hypertension in the Department of Cardiology of the Nanfang Hospital between January 2023 and December 2023. The diagnosis of hypertension was conducted based on the hypertension diagnostic criteria established by the World Health Organization and the International Society of Hypertension (WHO/ISH) in 1999. According to the 2018 European Hypertension Guidelines, patients were divided into three groups: low- and medium-risk hypertension group, high-risk group, and very high-risk group. There were 17 cases in the low- and medium-risk group, 37 cases in the high-risk group, and 31 cases in the very high-risk

group. The Score is a key indicator for assessing the 10-year risk of cardiovascular events in patients with hypertension. The Score of each patient can be calculated through the online website. According to the 2018 European Hypertension Guidelines, if the Score is≥10%, or if the patient suffers from severe chronic kidney disease (CKD), diabetes with target organ damage, vascular stenosis of more than 50%, or clinical cardiovascular disease (including ACS, stroke, etc.), then the patient is assessed as very high risk. If the Score scores between 5% and 10%, or if there is a significant increase in a single risk factor (especially cholesterol), stage 3 hypertension, diabetic patients without target organ damage, hypertension with left ventricular hypertrophy, moderate CKD, etc., patients are assessed as high risk. Patients with score scores between 1% and <5%, or stage 2 hypertension, are assessed as medium risk. Patients with score scores < 1% were assessed as low risk. This study has been approved by the Ethics Committee of Nanfang Hospital of Southern Medical University for conducting clinical research, and all enrolled patients have been fully informed of the research content and signed informed consent.。

1.2 Methods

This study used 16S rRNA technology to explore the changing characteristics of intestinal flora in hypertensive patients with different cardiovascular risk stratifications. First, stool samples of hypertensive patients with different cardiovascular risk stratifications (low-medium risk group, high-risk group, and very high-risk group) were collected. The samples were pretreated and the microbial genomic DNA was extracted. Then, the 16S rRNA gene was PCR amplified using specific primers. By sequencing the amplified products, a large amount of sequence information can be obtained. And these sequences represent different bacterial species. Then, the sequencing results were subjected to bioinformatics analysis. Including sequence quality control, removal of low-quality sequences and chimeras, etc. The high-quality sequences were clustered and divided into operational taxonomic units (OTUs). By comparing with known microbial databases, the bacterial species corresponding to each OTU can be determined.

Further analysis of the composition and diversity of the intestinal flora in hypertensive patients with different cardiovascular risk stratifications would be conducted. We compared the differences in indicators such as the richness and uniformity of the flora between the groups. At the same time, analysis of the changes in the relative abundance of specific bacterial groups in different groups was conducted. In addition, functional prediction analysis can also be performed to infer its possible metabolic functions and biological effects based on the composition of the flora. Through the above methods, we can gain an in-depth understanding of the changing characteristics of the intestinal flora in hypertensive patients with different cardiovascular risk stratifications, providing an important basis for further studying the relationship between intestinal flora and hypertension and its cardiovascular risk.

1.3 Statistic Analysis

In the study of the changing characteristics of intestinal flora in hypertensive patients with different cardiovascular risk stratifications based on 16S rRNA technology, statistical analysis plays a vital role. First, the collected clinical data of patients, such as age, gender, blood pressure, cardiovascular risk factors, etc., were analyzed using descriptive statistical methods to calculate statistical quantities such as mean value, standard deviation, and median to understand the distribution of basic characteristics of patients.

For the sequencing data of intestinal flora, statistical software was used for diversity analysis. The richness and uniformity of intestinal flora in patients with different cardiovascular risk stratifications were evaluated by calculating indicators such as Shannon index and Simpson index. Methods such as analysis of variance or non-parametric tests were used to compare whether the differences in these diversity indicators between different groups were statistically significant.。

The relative abundance of specific bacterial groups in the intestinal flora of different groups of patients is also compared and analyzed. Methods such as *t*-test and rank sum test can be used to determine whether the abundance changes of specific bacteria in different cardiovascular risk stratification groups are significant. In

addition, correlation analysis can be performed to explore the relationship between intestinal flora characteristics and clinical indicators such as patients' cardiovascular risk factors and blood pressure values. For example, methods such as Pearson correlation coefficient or Spearman correlation coefficient are used to analyze the correlation between the abundance of specific bacteria and variables such as blood pressure level and The Score.

Finally, to ensure the reliability of the results, multiple comparison corrections were performed, such as Bonferroni correction or False Discovery Rate (FDR) correction, to control the false positive rate. Through rigorous statistical analysis, the changing characteristics of the intestinal flora in hypertensive patients with different cardiovascular risk stratifications can be accurately revealed, providing strong support for a deeper understanding of the pathogenesis of hypertension and the search for potential therapeutic targets.

2 THEARY BASIS

2.1 The Technical Theory and Application of 16SrRNA Technology

2.1.1 The Advantage of 16S rRNA

16S rRNA technology has significant advantages in intestinal flora detection. Its high sensitivity can detect low-abundance microorganisms and even bacteria that are difficult to culture, making comprehensive analysis of intestinal flora possible. At the same time, the technology is highly specific and can accurately distinguish different types of bacteria, providing a strong guarantee for accurate identification of the composition of intestinal flora. In addition, the 16S rRNA gene is ubiquitous and relatively conservative in bacteria, making it easy to design universal primers for amplification and analysis.

2.1.2 Test Process

In the application of 16S rRNA technology, the detection process usually includes the following key links. The first is sample processing, collecting stool samples from patients and pre-processing them to extract high-quality microbial DNA.

Next is gene amplification, using specific primers to perform PCR amplification on specific regions of the 16SrRNA gene to obtain a sufficient number of target fragments. Then comes the sequencing step, using high-throughput sequencing technology to sequence the amplified products and obtain a large amount of gene sequence information. Finally, data analysis is performed, using bioinformatics methods to process and compare sequencing data to determine the characteristics of the intestinal flora, such as type, abundance, and diversity.。

2.2 Concept and Criteria of Hypertension in Cardiovascular Risk Stratification

2.2.1 classification Standards

The classification of cardiovascular risk stratification is mainly based on the patient's risk factors and target organ damage. Risk factors include age, gender, smoking, dyslipidemia, impaired glucose tolerance, etc. Target organ damage such as left ventricular hypertrophy and abnormal urine microalbumin also play a key role in stratification. In addition, concomitant clinical diseases such as heart disease and cerebral hemorrhage are also important considerations.

2.2.2 Standards

Hypertension in different risk stratifications has clear blood pressure ranges and related indicators. Low-risk patients usually only have stage 1 hypertension and no other risk factors. Medium-risk patients have 1-2 risk factors on the basis of low risk. High-risk patients have≥3 risk factors or target organ damage on the basis of low risk. Very high-risk patients have clinical comorbidities or diabetes on the basis of indicators of low risk. For example, stage 1 hypertension without risk factors is low risk. Stage 1 hypertension combined with 1-2 risk factors is medium risk. Stage 1 hypertension combined with≥3 risk factors or target organ damage is high risk. Stage 1 hypertension combined with clinical complications of diabetes is very high risk.

3 RESULTS

A total of 85 patients with essential hypertension were included in this study.

According to the 2018 European Hypertension Guidelines, they were further divided into low- and medium-risk hypertension group, high-risk group and very high-risk group. Among them, there were 17 cases in the low- and medium-risk hypertension group, 37 cases in the high-risk group, and 31 cases in the very high-risk group. The clinical data characteristics of the three groups of patients are shown in Table 1. The results showed that there were 10 male patients (58.8%) in the low- and medium-risk hypertension group, 22 male patients (59.5%) in the high-risk group, and 23 male patients (74.2%) in the very high-risk group. There was no statistically significant gender difference among the three groups (P=0.382). The average age of the low- and medium-risk group was 46.77±13.7 years old, the average age of the high-risk group was 53.38±14.54 years old, and the average age of the very high-risk group was 57.29±12.99 years old. The age difference among the three groups was statistically significant (P=0.047), and the very high-risk group was slightly older than the low- and medium-risk group. The average systolic blood pressure of the low- and medium-risk group was 144.41±15.64 mmHg, the average systolic blood pressure of the high-risk group was 152.87±21.55 mmHg, and the average systolic blood pressure of the very high-risk group was 160.55±18.68 mmHg. There was a statistically significant difference in systolic blood pressure among the three groups (P=0.025), and the systolic blood pressure of the very high-risk group was higher than that of the low- and medium-risk group. The average diastolic blood pressure of the low- and medium-risk group was 84±79/98 mmHg, the average diastolic blood pressure of the high-risk group was 90±78/105 mmHg, and the average diastolic blood pressure of the very high-risk group was 89±84/94.5 mmHg. There was no statistically significant difference in diastolic blood pressure among the three groups (P=0.465). The average BMI of the low- and medium-risk group was 25.27±2.9 Kg/m2, the average BMI of the high-risk group was 25.3±3.0 Kg/m2, and the average BMI of the very high-risk group was 25.4±2.89 Kg/m2. There was no significant difference in BMI among the three groups (P=0.988). The average fasting blood glucose in the low- and medium-risk group was 5.23±4.67/5.91mmol/l, the average fasting blood glucose in

the high-risk group was 5.28±4.78/6.46mmol/1, and the average fasting blood glucose in the very high-risk group was 5.5±5.13/6.76mmol/1. There was no significant difference in fasting blood glucose among the three groups (*P*=0.173). The average triglyceride in the low- and medium-risk group was 1.49±1.11/2.71mmol/1, the average triglyceride in the high-risk group was 1.47±1.13/2.41mmol/1, and the average triglyceride in the very high-risk group was 1.67±1.08/2.54mmol/1. There was no significant difference in triglyceride among the three groups (*P*=0.966). The average cholesterol in the low- and medium-risk group was 4.44±0. The average cholesterol level in the high-risk group was 4.71±1.02 mmol/1, and that in the very high-risk group was 4.35±1.07 mmol/1. There was no significant difference in cholesterol level among the three groups (*P*=0.315).

The average high-density lipoprotein in the low- and medium-risk group was 1.00 ± 0.94/1.15 mmol/1, the average high-density lipoprotein in the high-risk group was 1.07 ± 0.88/1.19 mmol/1, and the average high-density lipoprotein in the very high-risk group was 0.99 ± 0.82/1.05 mmol/1. There was no significant difference in high-density lipoprotein among the three groups (*P*=0.440). The average low-density lipoprotein in the low- and medium-risk group was 2.84 ± 2.45/3.05 mmol/1, the average low-density lipoprotein in the high-risk group was 2.98 ± 2.53/3.40 mmol/1, and the average low-density lipoprotein in the very high-risk group was 2.55 ± 2.07/3.10 mmol/1. There was no significant difference in low-density lipoprotein among the three groups (*P*=0.158).

The average serum creatinine in the low-medium-risk group was 68±61/82 mmol/1, the average serum creatinine in the high-risk group was 83±67/100 mmol/l, and the average serum creatinine in the very high-risk group was 85±72.5/120 mmol/1. The difference in serum creatinine among the three groups was statistically significant (*P*=0.017), and the serum creatinine in the very high-risk group was higher than that in the low-medium-risk group. There were no clinical complications in the low-medium-risk group and the high-risk group, and 31 patients in the very high-risk group had clinical complications. The difference in clinical complications among the

three groups was statistically significant (P<0.05). In summary, except for blood pressure, age, serum creatinine and clinical complications, there were no statistical differences among the groups (P<0.05).

Table 1 Clinical Characteristics of the Study Population

Items	Low-Mediate Risk(n=17)	High Risk(n=37)	Very High Risk(n=31)	Data($F/x^2/H$)	P
Male [(%)]	10(58.8)	22(59.5)	23(74.2)	1.925	0.382
Age (Year)	46.77±13.70	53.38±14.54	57.29±12.99*	3.183	0.047
systolic pressure (mmHg)	144.41±15.64	152.87±21.55	160.55±18.68*	3.875	0.025
diastolic pressure (mmHg)	84(79,98)	90(78,105)	89(84,94.5)	1.531	0.465
BMI (kg/m^2)	25.27±2.90	25.3±3.00	25.4±2.89	0.012	0.988
FBG (mmol/L)	5.23(4.67,5.91)	5.28(4.78,6.46)	5.5(5.13,6.76)	3.505	0.173
triglyceride (mmol/L)	1.49(1.11,2.71)	1.47(1.13,2.41)	1.67(1.08,2.54)	0.070	0.966
cholesterol (mmol/L)	4.44±0.78	4.71±1.02	4.35±1.07	1.173	0.315
high-density lipoprotein (mmol/L)	1.00(0.94,1.15)	1.07(0.88,1.19)	0.99(0.82,1.05)	1.640	0.440
low-density lipoprotein (mmol/L)	2.84(2.45,3.05)	2.98(2.53,3.40)	2.55(2.07,3.10)	3.691	0.158
serum creatinine (μmol/L)	64(61,82)	83(67,100)	85(72.5,120) *	8.178	0.017
Complications	0	0	31	/	/

Note: The X2 test indicator is: gender. The one-way ANOVA test indicators (normal distribution and homogeneity of variance): age, BMI, systolic blood pressure, total cholesterol. The Kruskal-Wallis test

indicators (not normal distribution): diastolic blood pressure, fasting blood sugar, serum creatinine, triglycerides, low-density lipoprotein, high-density lipoprotein. *P<0.05 vs. low-medium risk group.

4 The Association Mechanism between Changes in Intestinal Flora and the Progression of Hypertension

4.1 Gut Microbiota Metabolites and Blood Pressure Regulation

4.1.1 The Formation and Function of Metabolites

Intestinal flora can produce a variety of metabolites, among which short-chain fatty acids (such as acetic acid, propionic acid, and butyric acid) are an important category. These short-chain fatty acids are mainly produced by the fermentation of indigestible carbohydrates such as dietary fiber by intestinal flora. Short-chain fatty acids have many physiological functions, such as providing energy for intestinal epithelial cells, maintaining the integrity of the intestinal barrier, and regulating the acid-base balance of the intestine.

4.1.2 Specific Mechanisms of Blood Pressure Regulation

Short-chain fatty acids can affect the contraction and expansion of blood vessels, thereby regulating blood pressure. On the one hand, they can reduce the production of angiotensin II by inhibiting the activity of the renin-angiotensin-aldosterone system (RAAS), thereby leading to vasodilation and lowering blood pressure. On the other hand, short-chain fatty acids can stimulate endothelial cells to produce nitric oxide (NO), which is a powerful va`sodilator factor that can promote vasodilation and reduce peripheral vascular resistance, thereby playing a role in lowering blood pressure.

4.2 Gut Microbiota-Induced Immune Inflammatory Response and Hypertension

4.2.1 The Role of Immune Cells and Inflammatory Factors

In the relationship between the immune inflammatory response induced by intestinal flora and hypertension, specific immune cells such as macrophages and T cells play a key role. Macrophages can be divided into two subtypes, M1 and M2. M1 macrophages release pro-inflammatory factors, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), etc., to promote inflammatory response. M2 macrophages have anti-inflammatory effects. Helper T cells 17 (Th17) in T cells secrete inflammatory factors such as IL-17, exacerbating the inflammatory response.

4.2.2 The Link between Inflammation and Increased Blood Pressure

The imbalance of intestinal flora can lead to impaired intestinal barrier function, allowing bacterial toxins and metabolites in the intestine to enter the blood circulation, activate the immune system, and trigger a systemic chronic inflammatory response. This inflammatory state can lead to endothelial cell dysfunction, increase vascular permeability, and promote the formation of atherosclerosis. At the same time, inflammatory factors can also affect the activity of the renin-angiotensin system, leading to vasoconstriction and water and sodium retention, ultimately causing high blood pressure.

CONCLUSION

This study conducted an in-depth study of the intestinal flora of hypertensive patients with different cardiovascular risk stratifications based on 16S rRNA technology, and obtained a series of valuable findings. First, the results of the study showed that there were significant differences in the intestinal flora of hypertensive patients with different cardiovascular risk stratifications. The intestinal flora of patients in the low- and medium-risk groups differed from those in the high-risk and very high-risk groups in terms of composition and diversity. Specifically, the richness and uniformity of the intestinal flora of patients in the low- and medium-risk groups were relatively high, which may reflect that their bodies were in a relatively stable

state. The intestinal flora of patients in the high-risk and very high-risk groups showed varying degrees of changes, and these changes may be closely related to the increase in cardiovascular risk.

In terms of bacterial groups, specific bacterial species showed different relative abundances in different cardiovascular risk stratification groups. Some bacteria were relatively more abundant in the low- and medium-risk groups, but relatively reduced in the high- and very-risk groups. On the contrary, other bacteria increased significantly in the high- and very-risk groups. These changes may be due to the progression of hypertension and the increase in cardiovascular risk, which led to changes in the intestinal microenvironment and affected the composition of the intestinal flora.

Further analysis found that there was a certain correlation between changes in intestinal flora and patients' cardiovascular risk factors and clinical indicators. For example, the abundance of certain specific bacteria was positively or negatively correlated with blood pressure levels, The Score and other indicators. This suggests that intestinal flora may be involved in the development of hypertension and the regulation of cardiovascular risk through multiple pathways.

In addition, this study also provides a new perspective for a deeper understanding of the pathogenesis of hypertension. As an important part of the human microecological system, the intestinal flora has complex interactions with the host. The characteristics of intestinal flora changes revealed by 16S rRNA technology suggest that the intestinal flora may play an important role in the pathophysiological process of hypertension. For example, some intestinal bacteria may affect the host's blood pressure regulation mechanism, inflammatory response and cardiovascular function by producing specific metabolites.

In summary, this study successfully explored the changing characteristics of intestinal flora in hypertensive patients with different cardiovascular risk stratifications based on 16S rRNA technology. These findings provide an important basis for further studying the relationship between intestinal flora and hypertension,

and also provide potential targets for developing new hypertension treatment strategies. Future research can further explore the specific mechanism of action of intestinal flora in the pathogenesis of hypertension, as well as the feasibility of preventing and treating hypertension by regulating intestinal flora. At the same time, it can also be combined with other omics technologies and clinical studies to fully reveal the complex relationship between intestinal flora and hypertension and cardiovascular disease, and make greater contributions to improving the prevention and treatment of hypertension.

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