Specific Alterations of Gut Microbiota in Chinese Patients with Hypertension: A Systematic Review and Meta-Analysis

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\textbf{Keywords}
Gut microbiota · Hypertension · Blood pressure · China · Systematic review

\textbf{Abstract}
\textbf{Background:} China has the largest absolute burden of hypertension (HTN) in the world. Gut dysbiosis may be a potentially modifiable risk factor for HTN. However, the characteristics of gut microbiota in Chinese populations with HTN remain to be determined. \textbf{Methods:} We systematically searched for studies comparing the gut microbial in HTN with healthy controls in databases. The cut-off date was December 30, 2021. Semi-quantitative analysis and meta-analysis with standardized mean differences of the alteration in gut microbiota were carried out. \textbf{Results:} A total of 16 studies involving 2,372 patients with HTN and 849 controls were included, covering 16 Chinese provinces or regions. The present study supports that compared to healthy population, the diversity of patients with HTN is significantly compromised, while richness is overall preserved. To be specific, a significant increase of the Firmicutes (F)/Bacteroidetes (B) ratio is considered as a special parameter of gut microbiota in HTN patients. The increased abundance of phylum Firmicutes, genus \textit{Megasphaera}, \textit{Escherichia_Shogella}, and \textit{Klebsiella} while the lower abundance of phylum Bacteroidetes, genus \textit{Bifidobacterium}, \textit{Faecalibacterium}, \textit{Roseburia}, and \textit{Ruminococcus} may be associated with HTN. The gut microbial metabolism in HTN was more abundant in lipopolysaccharide biosynthesis, membrane transport, and steroid degradation. \textbf{Conclusions:} Variation in gut microbial parameters is likely associated with Chinese patients with HTN. Further investigations should distinguish geographical and ethnic characteristics to develop in-depth knowledge of the underlying mechanisms by which gut dysbiosis contributes to HTN.

\textbf{Introduction}
Hypertension (HTN), the major risk factor for the morbidity and mortality of cardiovascular disease [1, 2], is one of the top three risk factors contributing to the global burden of disease according to the data of 2017 Global Burden of Disease (GBD) [3]. Currently, China has the largest absolute burden of HTN in the world [4]. The prevalence of refractory HTN in hypertensive reach-
es 15%, raising an urgent need to find new targets for the therapy of HTN. However, the essential pathogenesis of HTN is not clear. Recently, plenty of evidence indicated that gut microbial dysregulation may be a potential risk factor for HTN, connecting with a number of diseases (cardiovascular disease, obesity, metabolic syndrome, and diabetes) [5–7]. In addition, along with the advance of the Brain-Gut-Bone Marrow Axis hypothesis, the dysfunctional brain-gut interactions in HTN were proposed [8].

Gut microbiota, also considered as an endogenous organ, has a complex community of almost a trillion microbial cells. It plays a crucial role in the maintenance of host health by supplying energy metabolism and immunological protection [9]. Both animal and epidemiological studies have provided strong evidence showing that alterations of the gut microbiota might be involved in the regulation of HTN [10]. Swapping the intestinal contents of normotensive Wistar-Kyoto and spontaneously hypertensive rats could induce or attenuate HTN [11, 12]. Alternatively, elevated blood pressure (BP) was observed both in germ-free rats [13] and transferrable germ-free mice through fecal microbiota transplantation from HTN human donors [14]. A high salt diet was verified to be a leading cause of HTN. The long-term high salt condition may perturb the gut microbiota and then promote HTN through igniting autoimmunity by inducing T helper 17 (TH17) cells, particularly, interleukin-17A (IL-17A)-producing CD4+ TH17 cells [15, 16]. In addition, gut microbiota produces, modifies, and degrades a large number of bioactive metabolites [17], including the primary and secondary bile acid, trimethylamine N-oxide, short-chain fatty acids (SCFAs), vitamins, amino acids, and p-cresyl sulfate, which contribute to HTN through various pathways (Fig. 1) [18–20]. Moreover, five large cross-sectional studies (TwinsUK, N = 2,737 [21]; CARDIA, N = 529
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Materials and Methods

Study Selection

This present study follows the preferred reporting project in the Systematic Review and Meta-Analysis (PRISMA) guidelines and was registered in the PROSPERO database (CRD42021238046). We systematically searched for literature including Observational and Randomized Controlled Trial (RCT) studies in PubMed, Web of Science, Cochrane, MEDLINE, and CAJD (Chinese Academic Journal Online Publishing Library) that compared the gut microbiome characteristics of hypertensive patients with controls from the study commencement date. Other inclusion criteria were original published studies using intestinal microbiome sequencing, describing gut microbiome characteristics of patients with high BP or HTN in the adult population (>18 years of age). Exclusion criteria were studies that focused on the association of diseases other than HTN, such as kidney disease, liver disease, sleep apnea, or oral microbiota. The literature search strategy included the intersection of hypertensive studies (Title, Keywords, Medical [Mesh] “Blood Pressure” or “Hypertension”) and microbiome studies (Title, Keywords, Gut Microbiota, Microbiota “Gut Microbiota”, [Mesh] “Microbiome”) (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.11159/000524282). Two reviewers (Qin and Zhao) screened the articles by title, abstract, and full-text view independently to ensure consistency. The literature search was conducted on December 30, 2021, without language and publication date restrictions.

Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa scale that contains eight-item scale, three dimensions of choice, comparability, and exposure. The scores ranging from 0 to 10 represent a gradual improvement in the quality of the studies included.

Data Extraction and Statistical Description

Key contents were extracted into a predesigned Excel containing characteristics of studies, analysis methods, sample collection, diversity comparison, distinct bacterial taxa, and functional characterizations of gut microbiota. Uncertain information was obtained by contacting the related authors.

For parameters with quantitative description, we extracted community-level measures of gut microbiota composition as the primary outcomes of interest. In community ecology, the α-diversity indices are applied to measure the species diversity (Shannon and Simpson indexes) and richness (Chao1 and ACE indexes) in the community, while β-diversity indices are used to measure the rate of species diversity change along the environmental gradient or the diversity between communities [26]. In this study, we extract the maximum, minimum, mean (M), and standard deviation of ACE, Chao1, Shannon, and Simpson indexes for data analysis. If the original data only provide the median and quartile range, we convert them to M and standard deviation based on web tools (http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html). If necessary, WebPlotDigitizer (v.4.4) was used to extract digital data from the figure. In pursuit of optimal accuracy of results, we performed a meta-analysis using Comprehensive Meta-Analysis version 2.0. The standardized mean differences (SMDs) and 95% confidence interval (CI) of the above indexes between the HTN and controls were calculated. Heterogeneity was represented by I². The fixed-effects model was used when I² ≤ 50% and the random-effects model was used when I² > 50%. Publication bias was evaluated with funnel plots and the Egger test. Two-sided p values were statistically significant at less than 0.05.

For the relative abundance of microbial taxa, we performed a semiquantitative analysis. An altered parameter was defined in our review [27] that if it changed in the same direction in more than two studies and there were no definite opposite results, the consequence was considered worth noting for future validation, whereas a consistent finding by three or more studies was considered potentially HTN-specific. Proportions (n/N) were used to present the alterations in gut microbiota profiles.

Result

Study Selection and Characteristics

A total of 692 potentially eligible articles were obtained from the literature search (Fig. 2). Fourteen case-control studies [14, 28–41], one prospective cohort study [14], and one cross-sectional study [24] met the inclusion requirements eventually after the standardized literature retrieval process, and no RCT studies were identified (Table 1). The total studies involved 2,372 patients with HTN and 849 controls, with the territorial scope covering 16 Chinese provinces or regions and the severity ranging from pre-hypertension (preHTN) to grade 3 HTN. One of the studies focused on altitude [34] and another focused on therapeutic effects [31]. The Newcastle-Ottawa scale showed four studies with a score of 5, nine with a score of 6, and three
with a score of 7, indicating a relatively high quality of the studies selected (online suppl. Table 2).

**Gene Analysis Methods and Sample Collection**

Based on the concept of selecting fecal flora as representative of intestinal flora, fecal samples were collected and analyzed in all studies (16/16) (online suppl. Table 3). Metagenomic shotgun sequencing or 16S ribosomal RNA (16S rRNA) gene sequencing were used in fifteen (15/16) studies to analyze the characteristics of gut microbiome. Five (5/16) studies mentioned the use of sample collection containers and twelve (12/16) studies mentioned the use of special conditions to accomplish sample transfer or storage.

**Bacterial Diversity of Gut Microbiota in Patients with HTN**

Bacterial diversity was analyzed in thirteen (13/16) studies [14, 24, 28, 30, 32–34, 36–41] (online suppl. Table 4). Of these assessments, seven (7/13) [14, 30, 34, 36, 37, 40, 41] provided data and were included in meta-analyses. We used bacterial diversity indexes (Shannon and Simpson indexes, Fig. 3) and richness indexes (Chao1 and ACE indexes, Fig. 4) to describe the results, respectively. There was significant difference in the SMDs of Shannon index between HTN and controls (SMD = −0.115, 95% CI = −0.227 to −0.003, p = 0.045, I² = 0.0%), while nonsignificant differences were found in Simpson, Chao1, and ACE indexes (SMD = 0.181, 95% CI = −0.107
Table 1. Characteristics of studies included in this review

| Reference   | Region          | Study design            | Disease          | Subject sample, n | Age (SD), years | SBP (SD), mm Hg | DBP (SD), mm | Treatment | The basic conclusion                                                                 |
|-------------|-----------------|-------------------------|------------------|-------------------|----------------|-----------------|--------------|-----------|---------------------------------------------------------------------------------------|
| Li et al.   | Tangshan, China | Prospective cohort study | preHTN            | preHTN 56         | 65±6.6         | 127.9±10.4     | 74±6.6       | Pre-HTN 94.7±9.2 | Prior to antihypertensive treatment                                                     |
| Yan et al.  | Harbin, China   | Case-control study      | HTN Con           | HTN 57.0±9.6      | 62±6.3         | 165±20          | 71±7         | HTN 101±11 | HTN implicated a remarkable gut dysbiosis with significant reduction in within-sample diversity and shift in microbial composition |
| Liu et al.  | Xianyang, China | Case-control study      | HTN Con           | HTN 56.8±6.6      | 71±7           | 149.8±14.2     | 72±6.9       | Pre-HTN 84.3±10.7 | Prior to antihypertensive treatment                                                     |
| Dan et al.  | Beijing, China  | Case-control study      | HTN Con           | HTN 57.7±6.2      | 74±6.9         | 145.9±13.4     | 72±6.9       | Pre-HTN 84.3±10.7 | Prior to antihypertensive treatment                                                     |
| Li et al.   | Henan, China    | Case-control study      | HTN Con           | HTN 58.4±10.2     | 73±6.4         | 149.8±11.6     | 72±6.9       | Pre-HTN 84.3±10.7 | Prior to antihypertensive treatment                                                     |
| Mushtaq et al. | Xi'an, China  | Case-control study      | Grade 3 HTN Con   | HTN 60.5±11       | 74±6.9         | 149.8±11.6     | 72±6.9       | AH: receive antihypertensive treatment                                                 |
| Chen et al. | Guangzhou, China| Case-control study      | Grade 3 HTN Con   | HTN 46.8±14.5     | 73±6.4         | 144.1±11.6     | 72±6.9       | AH: receive antihypertensive treatment                                                 |
| Zhu et al.  | Different altitudes in China (Qinghai-Tibet Plateau, Xining, Wuhan) | Case-control study | Grade 3 HTN Con   | HTN 56.5±13.0     | 74±6.9         | 144.1±11.6     | 72±6.9       | AH: receive antihypertensive treatment                                                 |
| Wang et al. | Henan, Hunan, Guizhou, Guangxi, China | Cross-sectional design | Cross-sectional Microbiota 1,003 Metabolomics 434 | N/A | N/A | N/A | N/A | The overall microbial community varied by BP                                                   |
| Lin et al.  | Qiqihar, China  | Case-control study      | Grades 1 HTN Con  | Grades 5.9±6.3    | 62±6.3         | 145.4±14.5     | 72±6.9       | N/A | Without receiving any antihypertensive drugs before sample collection                 |
| Wang et al. | Tangshan, China | Case-control study      | ISH IDH Con       | ISH 5.9±6.3       | 62±6.3         | 145.4±14.5     | 72±6.9       | ISH 80.3±75.8 | The disordered fecal bacteria profiles in subjects with ISH and especially IDH, emphasizing the significance of early intervention for IDH |
| Reference        | Region          | Study design      | Disease      | Subject sample, n | Age (SD), years | SBP (SD), mm Hg | DBP (SD), mm | Treatment                                      | The basic conclusion                                                                 |
|------------------|-----------------|-------------------|--------------|-------------------|----------------|----------------|-------------|------------------------------------------------|--------------------------------------------------------------------------------------|
| Wang et al. [37] | Chengdu, China  | Case-control study| HTN Con      | 93                | 15             | HTN 61.43±4.37  | Con 56.33±7.73 | HTN 144.69±9.29 | Con 113.60±9.00 | HTN 88.61±8.15  | Con 75.14±5.98 | N/A | Electroacupuncture can effectively lower BP and improve the structure of intestinal microbiota |
| Han et al. [38]  | Tangshan, China | Case-control study| HTN Con      | 28                | 14             | HTN 54.5 (50.75, 57.25) | Con 51.5, 60.6 | HTN 151.3 (140.75–160) | Con 120 (117.25–123.25) | HTN 96 (90–101) | Con 78 (72–80) | N/A | The reduction of indole acetic acid, a metabolite in the intestine of patients with HTN, is closely related to the disordered intestinal flora |
| Chen et al. [39] | Ningbo, China   | Case-control study| SSHT Con     | SSHT NSSHT       | 20             | SSHT 47.09±11.73 | NSSHT 46.09±19.59 | SSHT 147.6±13.62 | NSSHT 154.36±13.48 | SSHT 90.0±15.41 | NSSHT 86.73±9.58 | 73.45±6.28 | Lachnospira is the characteristic genus of intestinal flora changes in salt-sensitive HTN patients in Ningbo area |
| Liu et al. [40]  | Chengdu, China  | Case-control study| HTN Con      | 26                | 26             | HTN 56.9 (6.9)  | Con 50.1 (6.0) | HTN 140.9 (14.3) | Con 122.7 (13.2) | HTN 83.2 (8.2) | Con 77.7 (9.6) | Received different antihypertensive medications | This study aimed to determine the relationships among gut microbiota, primary aldosteronism |
| Wan et al. [41]  | Hangzhou, China | Case-control study| HTN Con      | 300               | 300            | HTN 61.60±11.92 | Con 62.02±11.79 | N/A               | N/A               | N/A               | The microbiome may serve as a biomarker to predict cardiovascular disease |

Con, control; HTN, hypertension; preHTN, pre-hypertension; NH, patients with treatment-naive hypertension; AH, hypertensive patients undergoing antihypertensive treatment; HLD, subjects with normal BP but with hyperlipidemia; LIG, low intermediate risk group; HG, high-risk group; VHG, very high-risk group; LH, the Han hypertensive from low-altitude (Wuhan: 13 m); MHH, the Han hypertensive living at middle-altitude (Xining: 2,260 m); HTH, the Tibetan hypertensive residing at high-altitude (Qinghai-Tibet Plateau: 3,600–4,500 m); LHN, the Han healthy individuals from low-altitude (Wuhan: 13 m); MHN, the Han healthy individuals living at middle-altitude (Xining: 2,260 m); HTN2, the Tibetan healthy individuals residing at high-altitude (Qinghai-Tibet Plateau: 3,600–4,500 m); ISH, isolated systolic HTN; IDH, isolated diastolic HTN; SSHT, salt-sensitive hypertension; NSSHT, nonsalt-sensitive hypertension; N/A, not available.
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Fig. 3. Bacterial diversity indices in the gut microbiota of HTN compared with healthy controls. LHH, the Han hypertensive from low-altitude; MHH, the Han hypertensive living at middle-altitude; HTH, the Tibetan hypertensive residing at high-altitude; ISH, isolated systolic HTN; IDH, isolated diastolic HTN.

to 0.470, \( p = 0.219, I^2 = 60.13\% \); SMD = 0.111, 95% CI = −0.025 to 0.247, \( p = 0.110, I^2 = 0.0\% \); SMD = 0.177, 95% CI = −0.115 to 0.469, \( p = 0.235, I^2 = 0.0\% \), respectively). Publication bias assessment for the α-diversity was shown in online supplementary Figure S1.

Ten (10/16) studies [14, 24, 30, 33, 34, 37, 39–41] measured the β-diversity of gut microbiota mainly using principal coordinate analysis or principal component analysis. Consistent differences between hypertensive and control were reported by eight (8/10) studies [14, 24, 30, 33, 34, 36, 40, 41]. Among them, Zhu’s study [34] confirmed a distinct difference among people with different altitudes whereas Wang’s study [37] and Chen’s study [39] found no differences between the two groups. Methods of measurement and patient classification may affect the consequence.
Relatively Distinct Bacterial Taxa in Patients with HTN

Seven (7/16) studies [28–30, 32, 34, 35, 37] described the distinct taxa at the phylum level, of which attentions were all paid to the microbiome analysis between HTN and control groups (Table 2). Six studies (6/7) [29, 30, 32, 34, 35, 37] demonstrated that the HTN group had higher abundant phylotypes of Firmicutes (F) while lower abundant phylotypes of Bacteroidetes (B), with an elevated F/B ratio. One study [28] suggested that Proteobacteria and Actinobacteria were the relatively distinct bacterial taxa at the phylum level.

Fourteen (14/16) studies [14, 28–34, 36–41] explored the distinct taxa at the genus level. A significantly higher richness of Megasphaera [30, 32, 40], Prevotella [14, 31, 32], and Escherichia_Shigella [32, 37, 41] was shown in HTN from three studies (3/14) respectively, while Klebsiella [14, 28] was confirmed with increased abundance in two (2/8) studies. Meanwhile, Roseburia [14, 28, 33, 38, 40] in five (5/14) studies, Faecalibacterium [14, 28, 31, 40] in four studies, and Bifidobacterium [14, 29, 31] in three studies identified a significant decrease in the abundance in HTN. Ruminococcus [30, 33] was also proved to be de-
| Reference       | Phylum level     | Family level     | Genus level     | Species level   |
|-----------------|------------------|------------------|-----------------|-----------------|
|                 | higher abundant  | lower abundant   | higher abundant | lower abundant  |
|                 | higher abundant  | lower abundant   | higher abundant | lower abundant  |
|                 | higher abundant  | lower abundant   | higher abundant | lower abundant  |
|                 | higher abundant  | lower abundant   | higher abundant | lower abundant  |
| Li et al. [14]  | N/A              | N/A              | N/A             | Faealbacterium, 
|                 | N/A              | N/A              | Prevotella, Klebsiella, 
|                 | N/A              | N/A              | Roseburia, Bifidobacterium, 
|                 | N/A              | N/A              | Coproaoccus, Butyrivibrio |
| Yan et al. [28] | Proteobacteria   | Actinobacteria   | Klebsiella, Clostridium, Streptococcus, Parabacteroides, Eggarthella, and Salmonella | Faealbacterium, Roseburia, and Synergistetes |
| Liu et al. [29] | Firmicutes       | N/A              | N/A             | N/A             |
| Dan et al. [30] | Firmicutes and   | Bacteroidetes    | Acetobacteroides, Alistipes, Bacteroides, Barnesiella, Butyricimonas, Christensenella, Clostridum, sensustricto, Casenella, Desulfovibrio, Dialister, Eisenbergiella, Faecalitales, Megasphaera, Micravirga, Mitsuokella, Parasabacterales, Proteinobacter, and Terrisporobacter | N/A             |
|                 | Bacteroidetes    |                  |                 |                 |
| Li et al. [31]  | N/A              | N/A              | N/A             | N/A             |
| Mushtaq et al. [32] | Firmicutes     | Bacteroidetes    | Prevotellaceae, Veillonellaceae, and Lachnospiraceae | Faealbacterium and Bifidobacterium |
| Chen et al. [33] | N/A              | N/A              | N/A             | N/A             |
| Zhu et al. [34] | Firmicutes       | Bacteroidetes    | Lachnospiraceae | N/A             |
| Wang et al. [24] | N/A              | N/A              | N/A             | N/A             |
| Lin et al. [35] | Firmicutes and   | Bacteroidetes    | LCH: Fusobacterium | N/A             |

Note: The table shows relatively distinct bacterial taxa in patients with HTN. The references are cited for each study to provide further information.
Table 2 (continued)

| Reference     | Phylum level | Family level | Genus level | Species level |
|---------------|--------------|--------------|-------------|---------------|
|               | higher abundant | lower abundant | higher abundant | lower abundant | higher abundant | lower abundant |
| Wang et al. [36] | N/A | N/A | N/A | ISH: Rothia | IDH: Faecalibacterium, Acetohalobium |
|               |              |              |             | ISH: Rothia mucilaginosa | |
| Wang et al. [37] | Firmicutes | Bacteroidetes | Lachnospiraceae | Bifidobacteriaceae | Escherichia, Shigella | Blautia | N/A | N/A |
| Han et al. [38] | N/A | N/A | N/A | N/A | Roseburia, Akkermansia, Subdoligranulum, Ruminiclostridium, Anaerotruncus, Intestinimonas, Pseudoflavonifractor, Paenibacillus, Haloterrabacter, Marvinbryantia, Onibacterium, Ruminococcus, Clostridium, Oscillibacter, Butyrivibrio, Pyramidobacter, and Acidiphilium | |
| Chen et al. [39] | N/A | N/A | N/A | Lachnospira, Villus | Parabacteroides | N/A | N/A |
| Liu et al. [40] | N/A | N/A | N/A | Megasphaera, Lactobacillus, Bacillus | Faecalibacterium, Subdoligranulum, Roseburia, Blautia | N/A | N/A |
| Wan et al. [41] | N/A | N/A | Enterobacteriales | Acidaminococcaceae | Escherichia, shigella | Phascolarctobacterium | N/A | N/A |

F/B, Firmicutes/Bacteroidetes; LHH, the Han hypertensive from low-altitude (Wuhan: 13 m); MHH, the Han hypertensive living at middle-altitude (Xining: 2,260 m); HTH, the Tibetan hypertensive residing at high-altitude (Qinghai-Tibet Plateau: 3,600–4,500 m); ISH, isolated systolic HTN; IDH, isolated diastolic HTN; N/A, not available.
creased in our study. Nevertheless, Dan’s study [30] revealed that the abundance of Prevotella was decreased, which was contrary to other studies above. The phylogenetic profile of differentially abundant taxa was shown in Figure S2.

Besides, four (4/16) studies [30, 32, 37, 41] and two (2/16) studies [32, 36] analyzed the distinct taxa at the family level and species level in bacterial scales, respectively. However, we did not find any relatively consistent results.

Functional Characteristics of Gut Microbiota in HTN

Four (4/16) studies [14, 24, 28, 36] employed the KEGG (Kyoto Encyclopedia of Genes and Genomes), CAZy (Carbohydrate-Active EnZymes) database, and pathway enrichment analysis to evaluate the functional characteristics of gut microbiota across groups in their study cohorts (online suppl. Table 5). Two of four studies [14, 28] using the KEGG analysis pointed out that HTN gut microbiomes were more abundant in lipopolysaccharide (LPS) biosynthesis, membrane transport, and steroid degradation.

Discussion

The treatment of HTN, especially refractory HTN, has reached a bottleneck stage at present. Gut microbiome, as one of the main mediums for the human body to exchange with environment, has been identified as a crucial factor involved in the pathogenesis and progression of HTN. The microbial ecosystem was formed in the embryonic period and modified under the action of many factors, including location, ethnicity, climate, diet, or age. Thus, we limited the scope of geographical location in this study to China. To our best knowledge, this is the first systematic review focusing on the microbiota perturbations in HTN in the particular region of China, which may provide a prospective viewpoint for optimal decision selection in clinical practice. Moreover, exploring the relationship between gut microbiota and disease epidemiology at the regional level is a critical part of public health science. The present study supports that, compared to the healthy population, patients with HTN have a significantly lower Shannon index of gut microbiota. To be specific, the increased abundance of phylum Firmicutes, genus Megasphaera, Escherichia_Shigella, and Klebsiella while the lower abundance of phylum Bacteroidetes, genus Bifidobacterium, Faecalibacterium, Roseburia, and Ruminococcus may be associated with HTN.

Our meta-analysis revealed a significant decrease in diversity indexes but a nonsignificant association with the richness indexes between HTN and controls, suggesting that although diversity is somewhat compromised, richness is overall preserved. In Guo’s observational analysis [25], the same conclusion was drawn that diversity was declining. Meanwhile, Zhu’s study proved significant differences in patients with different races, altitudes, and grades of HTN [34]. When it goes to subtypes of HTN, the bacterial communities in preHTN are different from the control group, but similar to the HTN group [14], suggesting that gut microbes may be involved in the progression of HTN. Chen’s study [33] investigated the changes of gut microbiota in patients with different cardiovascular risk stratified of HTN, drawing the conclusion that with the increase of cardiovascular risk, the abundance of probiotics in hypertensive intestines is significantly reduced. Moreover, patients with HTN displayed remarkable gut microbiota dysbiosis regardless of whether they received antihypertensive therapy [31]. These findings may further reveal that bacterial communities are closely related to the progression of HTN.

Analysis of gut microbiota taxa abundance could help identify the impacts on HTN. As we all know, the F/B ratio evolves during different life stages [42]. The bacteria of phylum Firmicutes produce high amounts of butyrate, whereas phylum Bacteroidetes lead to high levels of acetate and propionate [43]. Increasing evidence suggests that changes in the F/B ratio can be potentially used as a biomarker for pathological conditions [44–46]. In all the studies we included, the F/B ratio was consistently increased, which may be considered as a special parameter of hypertensive patients. Even more to the point, Yang et al. [45] demonstrated that minocycline therapy could recover the F/B ratio, remodel the microbiota composition, and achieve the goal of lowering BP. Understanding the influence of the F/B ratio and the fluctuations in microbiota composition may help to identify potential biomarkers for HTN [32].

The phylogenetic profile of the differentially abundant taxa showed that the expansion of genus Megasphaera may contribute to the increase of phylum Firmicutes (online suppl. Fig. S2), indicative of its marked alteration and a role in HTN. Megasphaera is known to synthesize SCFAs that affect host immune response and regulate intestinal homeostasis [47]. SCFAs can stimulate host G-protein-coupled receptor (GPR) pathways, resulting in the regulation of renin secretion and BP [6]. Studies using the vascular olfactory receptor (OLFR) 78 and GPR41 knockout mice further supported the involvement of gut dys-
bioso in BP control (Fig. 1). Communication between the enteric nervous system and the central nervous system, which is also affected by SCFAs, has similarly emerged with a potential link to BP. This ability of *Megasphaera* to produce SCFAs or to modulate the host’s immune system may be protective in attenuating disease during infection [48]. Although the abundance of *Megasphaera* was increased in our study, the level of SCFAs in patients with HTN was decreased [10, 25]. This suggests that the production of SCFAs may be affected by a combination of multiple bacteria in HTN. In addition, *Megasphaera* has been previously associated with bacterial vaginosis and pregnancy complications [49], and its role in HTN needs further exploration. *Escherichia_Shigella* is shown more abundant in patients with HTN, which is closely related to various afflictions including hemorrhagic colitis, septicemia, gastrointestinal tract inflammations, thrombocytopenia, IgA nephropathy, and hemolytic uremic syndrome through Shiga-toxins [50]. The exposure of *Escherichia_Shigella* is also associated with the activated NLRP3 inflammasome that excessively activates mucosal immunity [51]. Thus, we postulate that the expansion of pro-inflammatory *Escherichia_Shigella* would trigger a local or systemic mucosal immune response and result in HTN. Although three of our included studies suggested an increased abundance of *Prevotella* in hypertensive, the results are inconsistent and reports of that elsewhere are also controversial [5, 10, 52]. *Prevotella* in the gut plays a direct role in the beneficial response [53], which may improve glucose metabolism by promoting the glycogen storage process, supporting the importance of personalized approaches to improve metabolism [54]. However, it also has been linked to inflammatory conditions. The superoxide reductase and phosphoadenosine phosphosulfate reductase (PAPS) encoded by *Prevotella* may promote an inflammatory response in rheumatoid arthritis [55]. In addition, the inflammatory response also plays a critical role in chronic kidney disease [56]. Thus, we presume that through triggering the inflammatory response, *Prevotella* may play a critical role in the pathogenesis of HTN, which needs further exploration. As a common human intestinal pathogen, *Klebsiella* causes a range of diseases including pneumonia, urinary tract infections, or diarrhea. Besides, *Klebsiella* and *Escherichia_Shigella* can trigger the innate immune response through the production of LPS and elicit a subsequent inflammatory reaction which is mediated by the local generation of cytokines [20]. Interestingly, LPS biosynthesis has also been found to thrive in KEGG functional analysis of hypertensive gut microbiota (online suppl. Table 5). Therefore, we presume that the increase of *Klebsiella* may be responsible for HTN pathology. However, its role in the pathogenesis of HTN has been poorly reported.

The decreased abundance of *Faecalibacterium* and *Bifidobacterium* may be an important gut bacterial marker in HTN. When *Bifidobacterium* is cross-fed with other symbiotic microbiota like *Faecalibacterium*, the levels of SCFAs like butyrate in the gut can increase, potentially influencing host physiology in many aspects [57]. Previous evidence also proved that supplement of probiotics such as *Bifidobacteria* was associated with a lower prevalence of obesity [58] and a lower level of uremic toxins in CKD models [56]. Thus, the perturbed homoeostasis of *Bifidobacterium* and *Faecalibacterium* may reduce plasma SCFAs levels but elevate that of nephrotoxic toxins. The depletion of the genera *Roseburia* is another important conclusion in our study, which may result in less production of butyrate [59]. Butyrate, known for the effects of cardiovascular and renal protection [60], not only provides energy for the respiration of intestinal epithelial cells and maintains the integrity of the intestinal epithelium but also activates the differentiation of colonic regulatory T cells to suppress inflammation [61]. We also found genus *Ruminococcus* known for its cellulolytic ability as a key symbiont of the gut ecosystem [62] was reduced in patients with HTN. *Ruminococcus* plays a crucial role in the degradation and fermentation of dietary polysaccharides. The main fermentation metabolites of *Ruminococcus* are acetic acid and formic acid, and they are also considered as a major group of butyrate-producing Firmicutes phylum [43]. So, it is reasonable to suspect that reduction of *Ruminococcus* may also cause a series of physiological reactions in patients of HTN. Certainly, probiotic bacteria act in a variety of ways, including production of organic acids and antimicrobial compounds, improving gut barrier integrity and enzyme formation, modulation of immune and physiological function, as well as interaction with resident microbiota and the host [57], worth further investigation in the treatment of HTN.

Although the metabolite analysis in the included studies did not yield consistent results (online suppl. Table 6), functional analyses showed a strong association between microbial metabolites and BP, which may further support the role of gut microbiota in BP regulation [20, 24, 63]. The KEGG analysis showed that gut microbial metabolism in HTN was more abundant in LPS biosynthesis, membrane transport, and steroid degradation. While in Guo’s study [25] the upregulation pathways in HTN were LPS biosynthesis, phosphotransferase system, ABC transporters, etc. A nest-controlled study based on Chinese
HTN patients [63] highly emphasized the importance of amino acid metabolism in the development of HTN, especially phenylalanine, tyrosine, and tryptophan biosynthesis, aminoacyl-tRNA biosynthesis, and nitrogen metabolism pathways. In addition, compared with the control group, the gut microbial enzymes involved in SCFAs-producing enzymes were depleted, whereas the TMA-production was enriched in HTN patients, which reached the concordance with changes in the gut microbiome [28]. To sum up, current research conclusions on metabolism are not consistent, and further metabolic studies are likely to focus on these pathways to form new basics for the prevention and treatment of HTN.

Moreover, attention should be paid to the limitations. First, there is still a lack of evidence to identify pathogenic bacteria closely related to HTN because of the nature of observational studies, as well as the insufficient sequencing depth, differences in demographic characteristics, sequencing methods, sample sizes, and severity of HTN. A panoramic view of the gut microbiota could not be drawn from existing evidence. Second, our study failed to convert all qualitative data into quantitative data which may lead to certain heterogeneity of results. Finally, because of the substantially variable nature of evidence, it might be unable to conduct sensitivity analysis of all the results. Nevertheless, tracking individuals from preHTN to HTN and its complications including cardiac, renal, cerebrovascular, and retinal damage is a long process that requires long-term standardized follow-up. Functional studies and long-term follow-up studies are urgently needed to reveal the specific mechanisms by which gut dysbiosis contributes to HTN. The development in DNA technologies for microbial genomes manipulation, and the increasing knowledge of the molecular basis of diseases, combined with the advances in engineered smart bacteria, are promoting precise microbiome-based therapy for HTN [64].

Conclusions

The present study supports that there is a significant decrease of Shannon index in Chinese HTN patients while nonsignificant differences in Simpson, Chao1, and ACE indexes, indicating that compared to the healthy population, the diversity of patients with HTN is significantly compromised, while richness is overall preserved. To be specific, a significant increase of the F/B ratio may be considered as a special parameter of gut microbiota in HTN patients. The increased abundance of phylum Firmicutes, genus *Megasphaera, Escherichia_Shigella,* and *Klebsiella* while the lower abundance of phylum Bacteroidetes, genus *Bifidobacterium, Roseburia, Faecalibacterium,* and *Ruminococcus* may be associated with HTN. The gut microbial metabolism in HTN was more abundant in LPS biosynthesis, membrane transport, and steroid degradation. However, these findings should be prudently applied to the non-Chinese population. Further investigations should give full consideration to the influence of geographical and ethnical characteristics to develop in-depth knowledge of the underlying mechanisms between gut dysbiosis and HTN and explore the potential strategies for HTN prevention and treatment.

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Statement of Ethics

An ethics statement was not required for this study type; no human or animal subjects or materials were used.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study design: Y. Qin and S. Sun. Data acquisition and analysis: Y. Qin, J. Zhao, and Y. Wang. Modify the manuscript: M. Bai. Each of the authors contributed an important role in drafting the manuscript, accepting accountability, and ensuring the accuracy or completeness of the overall work is properly investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiry can be directed to the corresponding author.
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