


# Impact of Family Doctor Contract Services on Preventable Hospitalizations Amongst Patients with Hypertension in Rural China: Mediating Role of Primary Healthcare Quality

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**Purpose:** The objective of this study was to explore the connection between family doctor contract services and preventable hospitalizations. Additionally, we sought to examine the role of primary health care quality as a mediating factor in the link between family doctor contract services and preventable hospitalizations among patients with hypertension.

**Patients and Methods:** This cross-sectional study was performed in Dangyang (Hubei Province, Central China) and Xishui (Guizhou Province, Western China) counties in July–August 2023. Participants comprised 625 patients selected via a multi-stage sampling method. Causal mediation analysis was conducted to explore the effect of family doctor contract services on preventable hospitalizations and the mediating effect of primary healthcare quality on this relationship.

**Results:** Utilization rate of family doctor contract services of hypertensive patients was 58.6%, score of primary health service quality was 70.75 and incidence of preventable hospitalizations was 28.2%. Amongst hypertensive patients, utilization of family doctor contract services decreased the occurrence of preventable hospitalizations, with a total effect of  $-0.22$  ( $p < 0.001$ ). Primary healthcare quality mediates the association, with a mediate effect of  $-0.05$  ( $p < 0.001$ ), explaining 22.73% of the total effect.

**Conclusion:** Improving the utilization of family doctor contract services and primary healthcare quality may result in lower rates of preventable hospitalizations amongst hypertensive patients.

**Keywords:** family doctor contract services, preventable hospitalizations, primary healthcare quality, hypertension, mediation analysis

## Introduction

Recently, the incidence of chronic diseases has increased rapidly, with chronic non-communicable diseases becoming the leading cause of disease and mortality in China.<sup>1</sup> According to the Report on Nutrition and Chronic Diseases of Chinese Residents (2020), hypertension's prevalence rate in Chinese residents aged 18 and above is 27.5% (increasing),<sup>2</sup> seriously endangering population health. According to studies, hospitalizations can be prevented if hypertensive people have early access to qualified healthcare.<sup>3</sup> However, hypertension-caused preventable hospitalizations have increased in scale. In 2023, the total national health expenditure monitoring data showed 28.49 million discharged patients, with 2.52 million (8.85%) having chronic diseases could experience preventable hospitalizations. Total preventable hospitalizations cost for chronic diseases in China was \$26.27 billion (2023 exchange rate: RMB¥7.08 to US\$1.00) (8.63% of its hospitalizations cost). Cost of hypertension-caused preventable hospitalizations was \$4.21 billion (2023 exchange rate: RMB¥7.08 to US\$1.00), accounting for 16.02% of the total preventable hospitalizations cost for chronic diseases, leading to increased medical costs and resource wastage.<sup>4</sup> Thus, reducing preventable hospitalizations for hypertension is critical for healthcare policymakers, insurers and patients.

The family doctor contract service, implemented in China since 2012, aims to improve population health and enhance primary healthcare service quality by providing basic clinical care, public health services and health management through dedicated family doctor teams. The government encourages residents to voluntarily sign contracts with family doctor teams. Family doctors could offer various services to hypertensive patients (eg lifestyle guidance, health management advice, medication guidance, dietary counselling, exercise recommendations), helping the latter control their condition and improve their quality of life. The implementation of family doctor contract service is crucial to achieve full coverage of hypertension management and improve the rate of hypertension management.<sup>5</sup> Consequently, family doctor contract services may could reduce preventable hospitalizations amongst hypertensive patients.

Previous studies have shown that family doctor contract services can enhance primary healthcare quality.<sup>6,7</sup> Feng illustrated that contracted patients reported higher scores in the dimensions of primary care quality, including first contact-utilization, first contact-accessibility, continuity, coordination, comprehensiveness, family-centeredness and community orientation, compared with uncontracted patients after controlling for socio-demographic and service utilization factors.<sup>6</sup> Li found that the total Primary Care Assessment Tool score, continuity, comprehensiveness and family-centeredness are higher in patients who contracted General Practitioners(GPs) than those who did not.<sup>7</sup> Liu proved that the family doctor system can improve primary healthcare continuity amongst diabetics in urban China.<sup>8</sup> Systematic reviews have recognized the association between primary healthcare quality and preventable hospitalisation.<sup>9–11</sup> Lavoie proved that local access to extensive primary healthcare services is associated with lower preventable hospitalizations rates.<sup>12</sup> Improving primary healthcare services' accessibility, comprehensiveness and continuity can reduce preventable hospitalizations of patients with chronic diseases.<sup>13,14</sup> Van der Pol proved that higher achievement on some clinical quality measures of primary care is associated with reduced ambulatory care sensitivity conditions(ACSCs) emergency admissions.<sup>11</sup> Chen's research in China indicates that increased accessibility to primary health care is associated with reduced preventable hospitalizations,<sup>15</sup> and Zhao's research has found a negative relationship between the number of primary doctors and preventable hospitalizations for diabetes.<sup>16</sup> Besides, the increased primary healthcare resourcing was associated with decreased diabetes-related preventable hospitalizations rates.<sup>17</sup>

Evidence on whether family doctor contract services can reduce preventable hospitalizations remains limited. Several studies have explored this topic but yielded inconsistent results. In Australia, Ninh Thi Ha proved that preventable hospitalizations of patients with multiple conditions can be effectively reduced through regular family doctor contact.<sup>18</sup> She found that GP usage had a protective effect against the risk of preventable hospitalizations amongst diabetics.<sup>19</sup> The study found that the higher the regularity of GP contact, the lower the risk of preventable hospitalizations.<sup>18</sup> However, Sedigheh Salavati found no statistical relationship between access to family doctors and preventable hospitalizations in Iran.<sup>20</sup> Information is limited on the relationship between family doctor contract services and preventable hospitalizations in China. Studies from Taiwan have shown that the occurrence of preventable hospitalizations can be reduced through engagement in family practice nursing programs.<sup>21</sup>

Given the lower per capita income and healthcare resources in rural areas compared with urban areas,<sup>21,22</sup> the quality of primary health services enjoyed by rural hypertensive patients was lower and the economic burden of preventable hospitalizations was greater. Therefore, we set up our research site in the rural areas. We aim to investigate the impact of family doctor contract services on preventable hospitalizations amongst hypertensive patients and explore the mediating effect of primary healthcare quality on this relationship. Based on this, the study puts forward some policy suggestions to improve the quality of rural primary health services and reduce preventable hospitalizations of hypertensive patients. Realizing these objectives entails answering the following research questions:

1. What is the current utilization status of family doctor contract services, primary healthcare quality and preventable hospitalizations rate amongst hypertensive patients?
2. Do family doctor contract services reduce preventable hospitalizations amongst hypertensive patients?
3. Does primary healthcare quality mediate the association between family doctor contract services and preventable hospitalizations amongst hypertensive patients?

## Materials and Methods

### Study Design and Sample

This cross-sectional study was performed in Dangyang (Hubei Province, Central China) and Xishui (Guizhou Province, Western China) counties in July–August 2023. A multistage stratified cluster sampling was used to determine each county's hypertensive patient sample. In the first stage, two townships each that are relatively far away from and close to the county center were randomly selected in each county. In the second stage, in each township, two villages each that are relatively far away from and close to the township center were randomly selected. In the third stage, 20 hypertensive patients were randomly selected in each village. Inclusion criteria were as follows: (1) participants diagnosed with hypertension, (2) local residents aged at least 18 years, (3) participants capable of comprehending the questionnaire.

We identified 32 villages in Dangyang and Xishui, and 640 hypertensive patients were invited to participate (response rate: 100.0%). Cases with missing data or with wrong information were excluded. The final sample size was 625 (effective response rate: 97.66%) hypertensive patients.

Investigators were meticulously trained prior to the commencement of the study to ensure a comprehensive understanding of the questionnaire's content, a clear articulation of the research's objectives and significance, and a standardized approach to data collection. Consistency in the methodology of data entry was emphasized, and any responses deemed invalid or indicative of dishonesty were rigorously excluded to maintain the integrity of the dataset. Furthermore, a logical check was implemented to assess the consistency and rationality of the data. This process is instrumental in identifying potential discrepancies and outliers, thereby enhancing the overall quality and reliability of the research findings. The application of such stringent quality control measures ensures that the data collected is both accurate and reflective of the study's intended scope.

By the end of 2022, Xishui had a population of 584,100, its gross regional product (GRP) reached US\$3.616 billion (2022 exchange rate: RMB¥6.73 to US\$1.00) and per capita GRP of US\$6619.9. The county boasted 485 healthcare facilities, comprising 4498 beds and 4639 healthcare providers. Dangyang (Hubei Province, Central China) is a county-level city with population of 418,500 as of the end of 2022. In the same period, the city's GRP totaled US\$9.34 billion, with per capita GRP of US\$22317.38 (2022 exchange rate: RMB¥6.73 to US\$1.00). By the end of 2022, the city had 265 healthcare facilities, comprising 2454 beds and employing 3142 healthcare providers. In Xishui and Dangyang, healthcare facilities predominantly comprised county hospitals, township health centers and village clinics; township health centers and village clinics offer primary care services. County hospitals and township health centers provide outpatient and inpatient services. Each village clinic employed an average of 1–2 village doctors.

### Measures of Study Variables

#### Independent Variable: Family Doctor Contract Service

In China, patients are free to select their initial healthcare provider. Some patients opt to seek treatment directly at hospitals upon experiencing symptoms. Consequently, there are cases in which individuals have never utilized family doctor contract services. For this situation, the questionnaire included the following question: Have you ever used a family doctor contract service? Responses were used as basis to categories the participants into two groups: Those who had and had not utilized family doctor contract services.

#### Mediators: Primary Healthcare Quality

This study used Primary Care Assessment Tool for Adult Edition (PCAT-AE) as measurement instrument. PCAT-AE, developed by Johns Hopkins University (US), was designed to assess the characteristic functions of general practice as perceived by patients.<sup>22</sup> This research utilized the modified Chinese edition of PCAT-AE, which possesses good reliability and validity and is deemed suitable for evaluating China's primary healthcare.<sup>23</sup> Measurement dimensions include first visit utilization, accessibility, continuity, comprehensiveness, coordination, family-centered, community-oriented and cultural competency.

The scale comprises 8 dimensions and 24 items and uses a Likert 4 subscale (1 = "Never"; 2 = "Occasionally"; 3 = "Often"; 4 = "Always"); "Don't know or can't answer" serves as a neutral option with a 2.5 value. Each dimension's score is calculated as the average score of items within that dimension, whilst total score is the average of all dimensions.

Scale scores are converted to a 1–100 range by dividing each dimension's score by 4 and multiplying by 100, consistent with prior research.<sup>24</sup>

### Outcome Variables: Preventable Hospitalizations

The Agency for Healthcare Research and Quality (AHRQ) defines potentially preventable hospitalizations (PPHs) as those associated with such conditions as heart failure, diabetes, hypertension and asthma, for which effective primary care could likely avert hospitalizations.<sup>25</sup> Participants were initially queried on hypertension-caused hospitalizations within the past year. Village doctors, who are familiar with patients' hospitalizations experiences, were consulted to confirm preventable hospitalizations of hypertension based on Organization for Economic Co-operation and Development (OECD)'s inclusion and exclusion criteria. The specific criteria are as follows.

1. Inclusion criteria: age  $\geq 18$  years, main diagnosis: hypertension
2. Exclusion criteria: maternal cases, cases of death in hospital during admission, cases referred from other institutions, patients admitted and discharged on the same day

### Other Covariates

Several covariates were controlled for in the mediation model according to Anderson's model of health service utilization.<sup>26</sup> The following variables were included.

1. Tendency characteristics: Indicate inclination towards utilizing health services and encompass gender, age ( $<60$ ,  $\geq 60$ ), marital status (married, others), education level (no formal education, primary school, junior high school, high school and above) and BMI ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ,  $18.5 \text{ kg/m}^2 \leq \text{BMI} \leq 24.0 \text{ kg/m}^2$ ,  $\text{BMI} > 24.0 \text{ kg/m}^2$ ).
2. Capacity resources: Pertain to individuals' capacity to access health services and availability of health resources in their communities and households. They include annual household income, health insurance type and time taken to reach the nearest healthcare facility from home.
3. Need factors: Reflect individuals' characteristics based on health needs and include self-rated health status (good, normal, poor).

## Statistical Analysis

We conducted descriptive analyses to characterize the sample and performed linear regression to examine the correlation between family doctor contract services and primary healthcare quality. Logistic regression was utilized to explore the relationship between family doctor contract services and preventable hospitalizations, and that between primary healthcare quality and preventable hospitalizations. We utilized mediation analysis, modelling preventable hospitalizations outcomes as binary variables using probit regression models, including the mediator and covariates. To estimate the marginal total causal effect (TCE), natural direct effect (NDE) and natural indirect effect (NIE) through the mediators, we used the weighting approach outlined by Vansteelandt (2014).<sup>27</sup> Bootstrapping with 200 replications was applied to calculate 95% confidence intervals. Analyses were conducted in Stata/SE 18.0.

## Results

### Data Description

Table 1 presents the 625 respondents' demographic and health-related characteristics. Specifically, 52.32% and 47.68% resided in Xishui and Dangyang counties, respectively. Among them, women accounted for 56.6% of the overall respondents. 78.1% of the participants were over 60 years. Approximately half of the respondents had BMI either below (7.2%) or above (43.4%) normal. Additionally, 36.2% and 31.6% of the respondents self-reported their health conditions as good and poor, respectively. Among the participants, 42.7%, 21.1% and 8.6% of them had finished primary school, junior high school, and high school education or above, respectively. Notably, 27.7% of the respondents have not attended school. 14.1% and 50.6% of the participants had an average annual household income of less than \$706.2 and more than \$1412.4, respectively. Furthermore, 75.4% of the participants reported they could reach the nearest medical

**Table I** Respondents' Characteristics (n = 625)

Characteristics		N	%
Gender	Male	271	43.4
	Female	354	56.6
Age	<60	137	21.9
	≥60	488	78.1
Marital status	Be married	536	85.8
	Else	89	14.2
Educational level	Did not attend school	173	27.7
	Primary school	267	42.7
	Junior high school	132	21.1
	High school and above	53	8.6
BMI (kg/m <sup>2</sup> )	<18.5	45	7.2
	18.5–24.0	309	49.4
	>24.0	271	43.4
Self-assessment of health	Good	226	36.2
	Normal	202	32.3
	Poor	197	31.6
Annual household income (\$)	<706.2	88	14.1
	706.2 –1412.4	221	35.4
	>1412.4	316	50.6
Fastest time it takes to get to the nearest health care facility from home (min)	≤15	471	75.4
	>15	154	24.6
Family doctor contract services	Used	366	58.6
	Never used	259	41.4
Preventable hospitalizations	Occurred	176	28.2
	Never occurred	449	71.8
Primary healthcare quality (mean, SD)	Total points	70.75	13.15
	First-visit utilization	72.36	15.25
	Accessibility	56.94	21.63
	Continuity	89.75	14.31
	Comprehensiveness	71.73	15.76
	Coordination	56.25	19.90
	Family-centered	68.90	25.08
	Community oriented	66.71	21.87
Cultural competency	83.34	20.28	

**Abbreviation:** PPHs, potentially preventable hospitalizations.

**Table 2** Descriptive Statistics and Correlations Amongst Family Doctor Contract Service, Primary Healthcare and Preventable Hospitalizations

Variables	1	2	3
1. Family doctor contract Services	–		
2. Primary healthcare quality	0.36***	–	
3. Preventable hospitalizations	–1.08***	–0.95***	–

Note: \*\*\*p < 0.001.

**Table 3** Total and Indirect Effects of Family Doctor Contract Services on PPH Through Primary Care Quality (N = 625)

Outcomes	Parameters		95% CI		P
	Coefficients	SE	Lower	Upper	
Preventable Hospitalizations					
TE	–0.22	0.04	–0.28	–0.14	<0.001
NDE	–0.17	0.04	–0.25	–0.09	<0.001
NIE	–0.05	0.02	–0.08	–0.01	<0.001

facility from home in 15 minutes. Amongst the patients, 58.6% utilized family doctor contract services, whilst 28.2% experienced preventable hospitalizations. The calculated overall score for primary healthcare quality was 70.75.

## Correlation Analysis

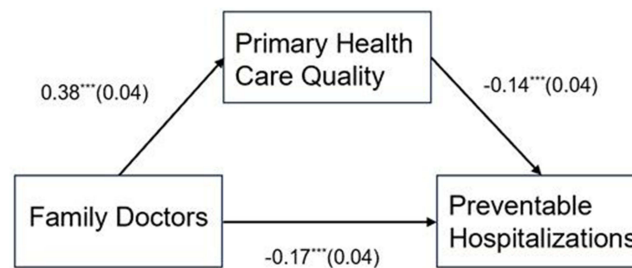
Table 2 shows a significant positive correlation between family doctor contract services and primary healthcare quality ( $p < 0.001$ ), indicating that higher utilization of such services is associated with better primary healthcare quality. Conversely, family doctor contract services showed negative correlation with preventable hospitalizations ( $p < 0.001$ ). That is, these services' increased utilization is linked to reduced preventable hospitalizations amongst hypertensive patients. Primary healthcare quality exhibited negative correlation with preventable hospitalizations ( $p < 0.001$ ), leading to further exploration of potential mediating effects.

## Model results and Analysis

Table 3 presents the results of testing the mediation model, which examined the relationship between family doctor contract services and preventable hospitalizations with primary healthcare quality as mediator. Note that total and specific indirect effects of family doctor contract services on preventable hospitalizations were significant. As shown in the Table 3, the total and mediating effects were  $-0.22$  ( $p < 0.001$ ) and  $-0.05$  ( $p < 0.001$ ), respectively. Direct effect constituted 77.27% of the total effect, whilst primary healthcare quality's mediating effect accounted for 22.73% of the total effect. Figure 1 illustrates that primary healthcare quality significantly mediates the association between family doctor contract services and preventable hospitalizations ( $p < 0.001$ ). These services were positively correlated with primary healthcare quality ( $\beta = 0.38$ ,  $p < 0.001$ ), which was negatively correlated with preventable hospitalizations ( $\beta = -0.14$ ,  $p < 0.001$ ).

## Discussion

Our study has yielded the following significant findings. First, in this study, the utilization rate of family doctor contract services of hypertension patients was 58.6%, the score of primary health service quality was 70.75, and the incidence of preventable hospitalizations was 28.2%. Secondly, family doctor contract services significantly reduced preventable hospitalizations amongst hypertensive patients. Thirdly, we identified the mediating effect of primary healthcare on the



**Figure 1** Mediation model of family doctor on preventable hospitalizations through primary health care quality (N = 625).

**Notes:** All numbers are unstandardized regression coefficients and their standard errors. \*\*\* $p < 0.001$ .

association between family doctor contract services and preventable hospitalizations amongst hypertensive patients (22.73% of the total effect).

As Chinese residents are free to choose their first-contact healthcare facility, a significant proportion of medical care seeking by residents is concentrated in large hospitals, giving rise to the problem of difficulty and costliness in accessing medical services among residents.<sup>28</sup> The purpose of implementing family doctor contract services is to promote the construction of hierarchical diagnosis and treatment system, improve the primary health care quality, reasonably control medical expenses and ultimately achieve the goal of “less illness, less hospitalizations, less burden and more health” of residents.<sup>29</sup> However, in this study, the utilization rate of family doctor contract services was relatively low, with only 58.6% of residents actually used the services. This result is consistent with previous studies.<sup>30–32</sup> In Qiu’s study, 95.3% of residents failed to make a referral, but went directly to secondary and tertiary hospitals.<sup>31</sup> This means that the function of family doctors in providing basic medical services and promoting referral was not fully developed. The low utilization rate of family doctor contract service may be due to insufficient incentive for family doctors’ team, patients’ distrust in family doctors and insufficient understanding of policy.<sup>31,33,34</sup> The primary health service quality score stands at 70.75, surpassing the metrics observed in prior urban Chinese studies; however, the dimensions of accessibility and coordination have registered comparatively lower scores.<sup>24</sup> The reason why the scores of accessibility are lower may be previous studies were conducted in urban areas while ours was conducted in rural areas, the transportation is less inconvenient and the Internet medicine have not been widely used. In terms of coordination, in rural areas, electronic medical records are not well applied and popularized and township health centers and upper-level hospitals lack an effective cooperation mechanism and in rural areas. Among the patients, 28.2% of hypertensive patients had preventable hospitalizations, which was relatively higher than previous studies.<sup>17,35</sup> This may be due to the generally older age of the patients in this study.

This study underscores family doctor contract services’ effect in significantly reducing preventable hospitalizations amongst hypertensive patients. This study underscores family doctor contract services’ effect in significantly reducing preventable hospitalizations amongst hypertensive patients. This observation aligns with the outcomes of an Australian study, which revealed that the engagement with general practitioners (GPs) conferred a protective influence against the risk of preventable hospitalizations in diabetic patients.<sup>19</sup> However, contrasting results were observed in a study conducted in Iran, where no statistically significant correlation was identified between accessibility to family doctors and the occurrence of preventable hospitalizations.<sup>20</sup> These discrepancies may be attributed to the variances in the quality of development and execution of family doctor contract services, which, in turn, can significantly influence the effectiveness of such programs. In our study, there was a negative association between family doctor contract services and preventable hospitalizations. This association can be attributed to the establishment of a fixed, contractual family doctor–hypertensive patient relationship. This relationship ensures that family doctors provide long-term, stable health guidance and management services tailored to patients’ needs. Services encompass the regular monitoring and control of patients’ blood pressure and provision of crucial health education, lifestyle advice and dietary guidance. This comprehensive approach ensures that patients receive continuous, systematic and holistic care.<sup>36</sup> These services enable hypertensive patients gain access to enhanced health knowledge, thereby improving their understanding of their condition. Consequently, they are likely to seek prompt treatment in illnesses’ early stages and obtain diagnoses and

treatments in primary care or outpatient settings, thereby mitigating preventable hospitalizations risks. Family doctors conduct follow-up visits with hypertensive patients, assessing their clinical status and determining whether hospitalization is necessary. This proactive approach further impacts preventable hospitalizations rates. Note that hypertensive patients' preventable hospitalizations in rural China can be reduced by using family doctor contract services, exerting a positive role in promoting and underscoring the significance of reducing preventable hospitalizations.

This study corroborates the significant mediating role of primary healthcare quality in the relationship between family doctor contract services and preventable hospitalizations amongst hypertensive patients. The mediating effect accounts for 22.73% of the total impact, highlighting the crucial linkage between these factors, which can be explained as follows. Firstly, family doctor contract services can improve primary healthcare quality based on the following aspects. Family doctors provide regular visits to follow up services and communicate with patients, which are conducive to mutual trust and improve primary healthcare's accessibility and continuity. The contracted service list covers basic public healthcare and clinical care services, ending the history of the public service delivery system's fragmentation and improving primary healthcare's comprehensiveness. Secondly, improving primary healthcare quality means more hypertensive patients will obtain effective diagnoses and treatments in primary healthcare facilities. Doctors will decide whether patients will be hospitalized according to their conditions, thereby effectively reducing the incidence of preventable hospitalisation.<sup>14,37</sup> Therefore, primary healthcare has an impact on reducing preventable hospitalizations.

Family doctor contract services play a pivotal role in reducing preventable hospitalizations amongst hypertensive patients, either through direct or indirect impact on primary healthcare quality. This study provides a policy basis for family doctor contract services. Firstly, the engagement of family doctor contract services plays a significant role in the reduction of preventable hospitalizations. While augmenting the engagement and utilization rates of family doctor contract services through strategic policy promotion and medical insurance guidance, it is imperative to concurrently expand the array of services offered by family doctors and to enhance the quality of care delivered. These strategic measures are instrumental in the reduction of preventable hospitalizations for patients with hypertension. Secondly, the primary healthcare services quality exerts an important mediating effect. To further reduce preventable hospitalizations, improving the quality of primary healthcare services should be regarded as a vital strategic intervention. This holds profound implications for alleviating the healthcare burden on rural hypertensive patients and fostering the equitable and judicious allocation of medical resources.

## Limitations of This Study

This study has several limitations. Firstly, the use of family doctor contract services was based on self-reported instead of recorded data, possibly having recall bias. However, such a bias was minimal because patients were asked to recall for only a year before the survey, following a previous study.<sup>6</sup> Future studies could use administrative and health insurance data on utilization of family physician contracted services and inpatient services to avoid recall bias. Secondly, this study focused on the potential mediating effect of the overall rather than the dimensions of primary healthcare quality. Further studies may be needed to confirm which primary healthcare quality dimensions play potential mediating roles. In future studies, structural equation models can be established on the basis of existing studies to verify which dimension plays a mediating role.

## Conclusion

Our research underscores the effectiveness of utilizing family doctor contract services in reducing the incidence of preventable hospitalizations. Primary healthcare quality potentially mediates this relationship (22.73% of the total effect). To address these findings, measures are needed to enhance the utilization of family doctor contract services. Effort should be directed towards improving primary healthcare quality in China's rural areas. Through proactive steps to encourage the utilization of family doctor contract services and bolster primary healthcare quality, we can effectively reduce preventable hospitalizations and improve rural communities' overall healthcare outcomes.

## Data Sharing Statement

This study's dataset is available from the corresponding author on a reasonable request.

## Ethics Approval

The study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology, with ethics approval number of IORG0003571. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all participants. This study complies with the Declaration of Helsinki.

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## Disclosure

The authors declare they have no competing interests.

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