

# Current status of diagnosis and treatment of pulmonary hypertension in Chinese tertiary hospitals: A nationwide survey

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## Abstract

We intended to evaluate the diagnosis and treatment status of pulmonary hypertension (PH) in China and provide the basis for the design of the Chinese PH centers system. A questionnaire survey was conducted by sampling from Chinese Class A tertiary hospitals that have carried out the clinical work of PH, including the composition of PH clinical team, the current application of examinations related to PH diagnosis, the availability of PAH-specific medicine and the implementation of PH-related intervention and surgery. A total of 44 valid questionnaires from 20 provinces were collected in this survey. In the vast majority of centers (83.33%,  $n = 35$ ), pulmonary artery catheterization was routinely performed under X-ray guidance. In 19.05% ( $n = 8$ ) of centers, pressure measurements were determined at the right time (the end of normal expiration). Only 73.81% ( $n = 31$ ) centers have carried out acute vasoreactivity testing. Prostacyclin analogues and prostaglandin receptor agonists were just prescribed in 45.45% ( $n = 20$ ) of the centers. 19 centers (43.18%) were capable of performing balloon pulmonary angioplasty (BPA) and pulmonary endarterectomy (PEA), while 25% ( $n = 11$ ) were able to perform BPA, PEA, and lung transplantation. There was no significant difference in the diagnosis and treatment of PH between economic regions. The majority of Chinese tertiary hospitals were well equipped with the corresponding personnel, examinations and medicines related to PH, but

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the standardization and specialization of the management of PH need to be strengthened.

**KEYWORDS**

diagnosis, pulmonary hypertension, survey, treatment

## INTRODUCTION

Pulmonary hypertension (PH) is a progressive and fatal disease with high morbidity and mortality. PH features structural and functional changes in the pulmonary vasculature caused by multiple etiologies, leading to elevated pulmonary vascular resistance (PVR) and pulmonary arterial pressure, inducing right heart failure or even death.<sup>1</sup> Misdiagnosis and delay of treatment are common in PH patients because of their diverse etiologies, complex pathogenesis, and nonspecific clinical manifestations. In Europe and the United States, PH centers are set up to figure out the dilemma of PH diagnosis and treatment,<sup>1,2</sup> which are defined by a set of criteria: (1) the annual number of PH patients is no fewer than 200 cases and the annual follow-up number of PAH or CTEPH patients is no fewer than 50 cases; (2) the annual number of acute vasoreactivity test (AVT) should be no less than 20 cases; (3) a multidisciplinary team and specialized wards should be equipped; (4) PH-related diagnostic techniques and drugs should be available.<sup>1,3-5</sup>

In recent years, great progress in PH clinical area has been made in China, but still several problems remain to be solved, such as insufficient multidisciplinary collaboration, inappropriate treatment, inadequate consultation, delayed referral and so on.<sup>6</sup> In China, the medical insurance system and medical-seeking pattern are different from those in Western society, so how to build up PH centers in China is an urgent problem to be solved.

To clarify the problems in the construction of the Chinese PH Center, a survey on the current status of PH diagnosis and treatment ability in Chinese medical institutions was jointly initiated by the Group of Pulmonary Embolism and Pulmonary Vascular Disease of Chinese Thoracic Society, Working Committee of Pulmonary Embolism and Pulmonary Vascular Disease of Chinese Association of Chest Physicians, National Project of Standardized Diagnosis and Treatment of PH. The results of the survey will provide a basis for the subsequent standard settings of PH centers in China.

## METHODS

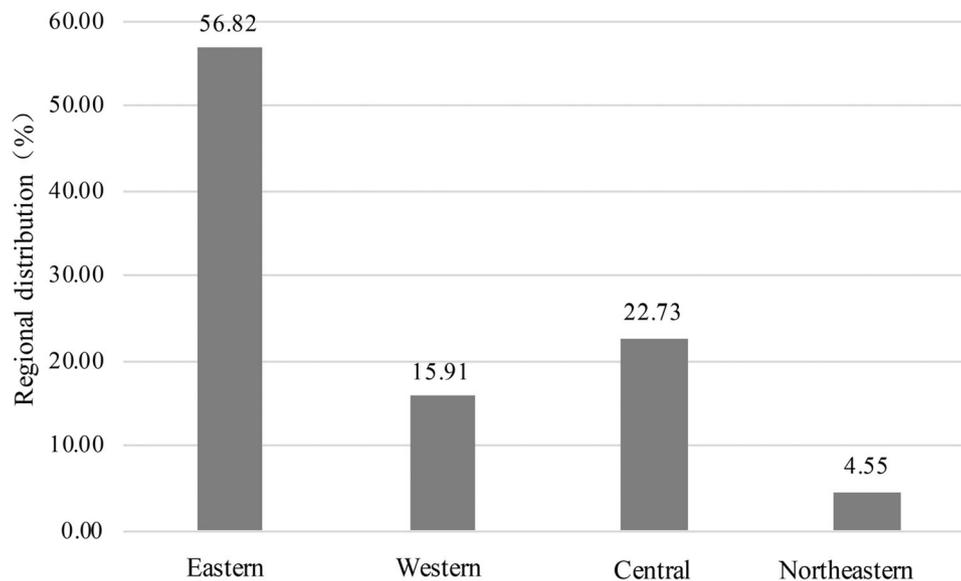
By utilizing convenience sampling, the electronic questionnaire was distributed to the members of the Group of Pulmonary Embolism and Pulmonary Vascular Disease of the Chinese Thoracic Society, Working Committee of Pulmonary Embolism and Pulmonary Vascular Disease of the Chinese Association of Chest Physicians, National Project of Standardized Diagnosis and Treatment of PH by email and WeChat from August 2021 to October 2021. Most of members of these three associations all work in Class A tertiary hospitals, which are generally regional medical centers, representing the highest level of medical care in the region. Rather than focusing on one department, we surveyed the diagnosis and treatment of PH throughout the whole hospital. All participants completed an online informed consent form.

The questionnaire included 20 questions based on 4 aspects: the composition of the PH clinical team, the current application of examinations related to PH diagnosis, the availability of PAH-specific medicine and the implementation of PH-related intervention and surgery. All hospitals were divided into 4 groups based on the regional economic segmentation method of the National Bureau of Statistics, which are eastern, western, central, and northeastern regions. All the statistical analysis was performed utilizing IBM SPSS 26.0. The data were analyzed utilizing a descriptive statistical method. The categorical data were expressed as n (%). Comparison of different subgroups was accomplished with the Chi-squared test or Fisher's exact test. Differences were considered statistically significant at  $p < 0.05$  (two-sided test).

## RESULTS

### General characteristics

A total of 70 electronic questionnaires were sent out and 44 valid questionnaires were obtained from 20 provinces and the municipality directly under the central government of China, with a response rate of 62.9%. All hospitals were Class A tertiary hospitals and covered all



**FIGURE 1** Regional distribution of hospitals surveyed.

**TABLE 1** The composition the of PH clinical team.

Variables	n (%)
Equipped with specialist nurses in pulmonary vascular disease with intermediate and senior titles or not	
Yes	40 (90.90)
No	4 (9.09)
Equipped with radiologists and sonographers in pulmonary vascular disease with intermediate and senior titles or not	
Yes	43 (97.72)
No	1 (2.27)
Set up PH-specific clinics or not	
Yes	30 (68.18)
No	14 (31.82)

Abbreviation: PH, pulmonary hypertension.

economic regions of China, most of which were from the eastern region ( $n = 25$ , 56.82%) (Figure 1).

### The composition of the PH clinical team

Our survey observed that 90.90% ( $n = 40$ ) of the hospitals were equipped with specialist nurses in pulmonary vascular disease with intermediate and senior titles, and 97.72% ( $n = 43$ ) were equipped with radiologists and sonographers with intermediate and senior titles qualified to diagnose pulmonary vascular diseases (Table 1).

There were 68.18% ( $n = 30$ ) of hospitals with PH-specific outpatient clinics (Table 1).

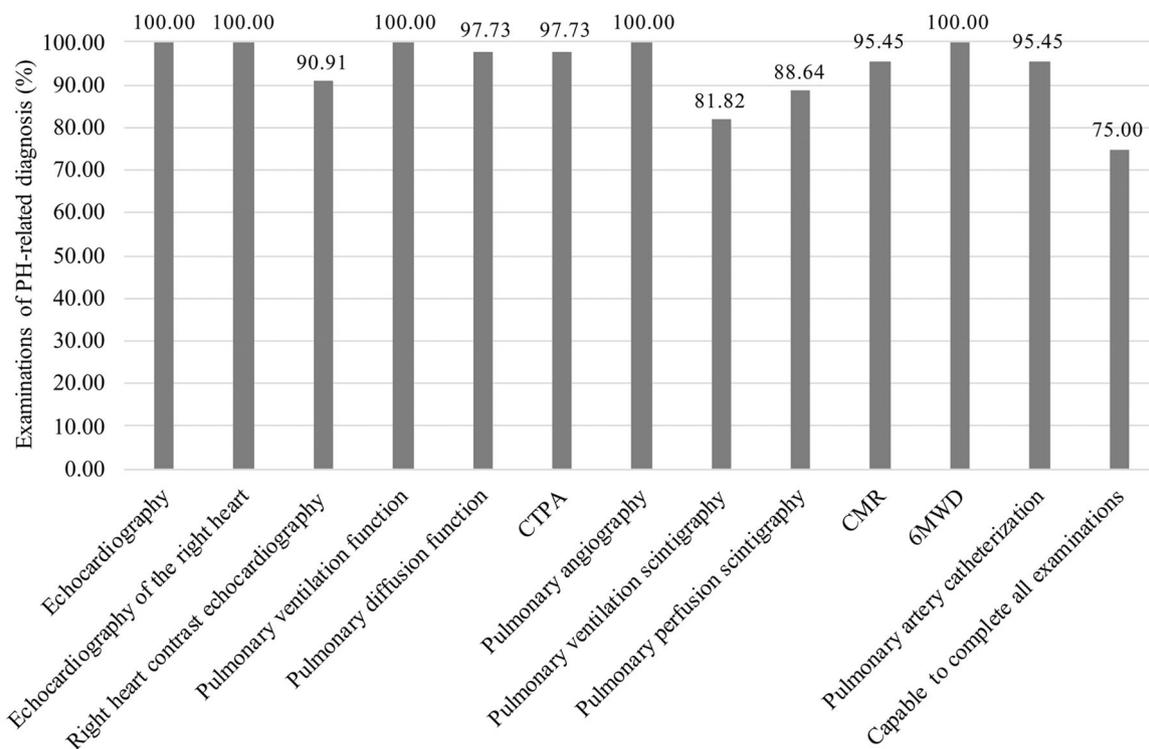
### The current application of examinations related to PH diagnosis

Among the hospitals participating in this survey, 75% ( $n = 33$ ) were equipped with all the examinations related to PH diagnosis. Of them, pulmonary ventilation scintigraphy (81.82%,  $n = 42$ ), pulmonary perfusion scintigraphy (88.64%,  $n = 39$ ) and right heart contrast echocardiography (90.91%,  $n = 40$ ) were the least-configured examinations relevant to the diagnosis of PH (Figure 2).

Pulmonary artery catheterization (PAC) was performed under X-ray guidance in most hospitals (83.33%,  $n = 35$ ). The internal jugular vein (88.10%,  $n = 37$ ) and femoral vein (54.76%,  $n = 23$ ) were the most frequently used catheter access routes for PAC. Only 47.62% ( $n = 20$ ) of hospitals performed pressure measurements at end-expiration, while a considerable percentage of hospitals (61.9%,  $n = 26$ ) measured pressures during free breathing. In less than half of hospitals (47.62%,  $n = 20$ ), complete data on PAC could not be acquired. AVT could be performed in only 73.81% ( $n = 31$ ) of hospitals, of which 70.97% ( $n = 22$ ) operated more than 20 cases per year. The most widely used drug for AVT was iloprost (87.10%,  $n = 27$ ) in China. Eleven hospitals (35.48%) used adenosine as the AVT drug (Table 2).

### The availability of PAH-specific Medicine

A total of 88.64% ( $n = 39$ ) of the hospitals could prescribe phosphodiesterase type 5 inhibitors (PDE-5i), soluble



**FIGURE 2** The status of examinations related to PH diagnosis. CMR, cardiac magnetic resonance; CTPA, computed tomography pulmonary angiogram; PH, pulmonary hypertension; 6MWD, 6-minute walking distance.

guanylate cyclase agonists (sGC) or endothelin receptor antagonists (ERA) in their own prescribing systems. 45.45% ( $n = 20$ ) of the hospitals could prescribe prostacyclin analogues and prostaglandin receptor agonists; only 40.91% ( $n = 18$ ) of hospitals were able to prescribe PAH-specific medications that targeted all three pathways (Table 3).

### The implementation of PH-related intervention and surgery

68.19% ( $n = 30$ ) of the hospitals were capable of performing balloon pulmonary angioplasty (BPA), with 26.67% ( $n = 8$ ) of them performing over 50 cases per year. Among the 21 hospitals that could perform pulmonary endarterectomy (PEA) (47.73%), only 4 (19.05%) performed more than 20 cases per year. 19 hospitals (43.18%) could perform lung transplantation, with 9 hospitals (47.37%) performing more than 10 cases per year. Both BPA and PEA were available in 19 hospitals (43.18%). Only 25% ( $n = 11$ ) of hospitals could perform all three procedures while 20.45% ( $n = 9$ ) could not do either (Table 4).

### Comparisons between different economic regions

There were no statistically significant differences between different economic regions in the development status of PH-related examinations and procedures, the standardization of PAC and the accessibility to PAH-specific medications (Table 5).

### DISCUSSION

In this cross-sectional study, we explored the current status of PH diagnosis and treatment abilities in China. Questionnaires were collected from 20 provinces across all economic regions of China. Therefore, the survey data had a good representative of the current status of PH management in China and offered meaningful insight into practice across the nation. In a comparison of groups according to different economic regions, there were no significant differences could be observed, suggesting that the levels of diagnosis and treatment of PH in different regions are relatively balanced.

The multidisciplinary team in a PH center can provide better care for PH patients. In our study, good

**TABLE 2** The current status of pulmonary artery catheterization.

Variables	n (%)
PAC was performed under X-ray guidance or not	
Yes	35 (83.33)
No	9 (20.45)
Catheter access routes for PAC	
Internal jugular vein	37 (88.10)
Femoral vein	23 (54.76)
Median cubital vein	6 (14.29)
Subclavian vein	10 (23.81)
Antebrachium veins	4 (9.52)
Time for pressure measurement	
Free breathing	26 (61.90)
End-expiration	20 (47.62)
End-inspiration	7 (16.67)
Hold breath	5 (11.90)
The PAC data could be obtained	
mPAP	42 (100.00)
CO (Fick)	28 (66.67)
CO (thermodilution)	28 (66.67)
PAWP	40 (95.24)
PVR	38 (90.48)
Pressure measurement of right heart system	35 (83.33)
Differences of oxygen saturation of right heart system	35 (83.33)
Analysis of pressure waveform	32 (76.19)
All data above are available	20 (47.62)
Acute vasoreactivity testing	
Capable to perform AVT	31 (73.81)
≥20 cases per year	22 (70.97)

Abbreviations: AVT, acute vasoreactivity testing; CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAC, pulmonary artery catheterization; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

participation of radiologists, sonographers and nurses could be observed. And more than 90% of the hospitals are staffed with corresponding personnel. Additionally, in the PH specialized outpatient clinic, a comprehensive and multidisciplinary PH care is provided. Hence, PH specialized outpatient clinic is considered to be a sign of PH diagnosis and treatment specialization. However, our study showed that only 68.18% of the hospitals had them. According to the above findings, it can be concluded that

**TABLE 3** The accessibility to PH therapeutic agents.

PAH-specific drugs	n (%)
PDE5i and sGC agonists	39 (88.64)
Sildenafil	32 (76.19)
Tadalafil	29 (65.91)
Riociguat	14 (31.82)
ERAs	39 (88.64)
Bosentan	28 (63.64)
Ambrisentan	27 (61.36)
Macitentan	25 (56.82)
Prostacyclin analogues and prostaglandin receptor agonists	20 (45.45)
Treprostinil	16 (36.36)
Iloprost	8 (18.18)
Selexipag	14 (31.82)
Access to PAH-specific drugs targeted three pathways	18 (40.91)

Abbreviations: PDE-5i, phosphodiesterase type 5 inhibitor; sGC, soluble guanylate cyclase.

**TABLE 4** The status of PH-related intervention and surgery.

Variables	n (%)
BPA	
Capable to perform BPA	30 (68.19)
≥50 cases per year	8 (26.67)
PEA	
Capable to perform PEA	21 (47.73)
≥20 cases per year	4 (19.05)
Lung transplantation	
Capable to perform lung transplantation	19 (43.18)
≥10 cases per year	9 (47.37)
Capable to perform all three technologies	11 (25.00)
None of the above technologies can be performed	9 (20.45)

Abbreviations: BPA, balloon pulmonary angioplasty; PEA, pulmonary endarterectomy; PH, pulmonary hypertension.

the structure of the PH specialized team in China was similar to the international situation, which can basically meet the existing demand for diagnosis and treatment of PH. However, the specialization of PH diagnosis and treatment still needs to be improved.

In this study, we also investigated the diagnostic capacity of PH in Chinese tertiary hospitals. Regarding the availability of diagnostic tests of PH, we found that

TABLE 5 Comparisons between different economic regions.

Variables	Eastern (n = 25)	Central (n = 7)	Western (n = 10)	Northeastern (n = 2)	p Value
All diagnostic tests related to PH could be performed, n (%)	17 (68.00)	6 (85.71)	8 (80.00)	1 (50.0)	0.586
Time for pressure measurement was selected correctly, n (%)	12 (48.00)	5 (71.43)	2 (20.00)	0 (0.00)	0.200
All data of PAC could be obtained, n (%)	11 (44.00)	1 (14.29)	4 (40.00)	2 (100.00)	0.185
AVT could be performed, n (%)	17 (68.00)	6 (85.71)	6 (60.00)	0 (0.00)	0.210
Access to prostacyclin analogues and prostaglandin receptor agonists, n (%)	12 (48.00)	3 (42.86)	3 (30.00)	0 (0.00)	0.601
Access to PAH-specific drugs targeted three pathways, n (%)	10 (40.00)	3 (42.86)	3 (30.00)	0 (0.00)	0.767
Capable to perform all three technologies, n (%)	4 (16.00)	3 (42.86)	2 (20.00)	0 (0.00)	0.405
Capable to perform PEA and BPA, n (%)	10 (40.00)	3 (42.86)	4 (40.00)	0 (0.00)	0.874

Abbreviations: AVT, acute vasoreactivity testing; PAC, pulmonary artery catheterization; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

most of the hospitals surveyed were well equipped with PH diagnostic facilities, and more than 95% could perform cardiac MRI and PAC. PAC is not only the gold standard for confirming the diagnosis of PH, but also an important tool for differential diagnosis, assessing the severity of the disease and treatment effect. Therefore, in this study, we also investigated the standardization of PAC. The results showed that the majority of hospitals performed PAC using conventional X-ray guidance (83.33%,  $n = 35$ ). Under the guidance of the balloon, the PAC could be completed by observing the pressure waveform without the X-ray guidance. Although X-ray guidance could improve the efficiency of the operation, it could also increase radiation exposure. Therefore, the indications for X-ray guidance needed to be strictly limited. Moreover, our study found that 61.9% of hospitals measured pressures during free breathing, not at the end of expiration. As the results may be significantly influenced by swings in the intrathoracic pressure and this effect is least pronounced at the end of a normal expiration, the international guidelines on PH clearly recommend that all pressure measurements should be determined at the end expiration.<sup>1,7</sup> Ignoring the effect of the respiratory cycle on pressure measurements may reduce the accuracy of hemodynamics and repeatability of measurements, thereby affecting the hemodynamic classification and diagnosis.<sup>8</sup>

In addition, we observed that a considerable percentage of hospitals could not perform AVT. According to the criteria of PH centers in Europe and the United States, the number of AVT cases should not be less than 20 per year.<sup>1</sup> However, the results of our study indicated that less than half of the hospitals could meet this standard. The low accessibility of AVT drugs might be a contributing factor. Currently, inhaled iloprost is the most widely used drug for AVT in China, but it is still difficult to access in many areas. Adenosine is easy to access, however severe adverse effects due to systemic vasodilator effects and its use requires titration to a maximal dose. The above disadvantages limit the clinical application of adenosine. Inhaled nitric oxide is recommended as one of the AVT drugs in both the European and American guidelines, but it is not approved for clinical use in China. As a result, it is imperative to broaden access to AVT drugs in China.

With the promotion of the government and academic organizations, the accessibility of PAH-specific drugs has been greatly improved in China. According to the European and American PH guidelines, prostacyclin analogues are recommended for the treatment of patients with advanced PAH.<sup>1,9</sup> The lack of prostacyclin analogues significantly impacted the rate of successful treatment for severe PAH. The criteria for PH centers

developed by PH Association specifically emphasize that PH centers must have adequate experience prescribing and managing parenteral prostanoid infusions: managing  $\geq 20$  infusion patients over the preceding 3 years.<sup>4</sup> Despite all this, their use is frequently delayed and, in many cases, they are not used at all. The data from the REVEAL study suggested that in the PAH-related death cohort, only 56.0% received intravenous prostacyclin before death and only 57.7% of patients with functional class IV received prostacyclin analogues.<sup>10</sup> In line with the previous studies, our study also observed that drugs targeting the prostacyclin pathway were available in less than 50% of hospitals, indicating that these drugs were still underused in clinical practice. Therefore, standardized medication, especially the intravenous use of prostacyclin drugs in severe patients, should be paid more attention.

BPA, PEA, and lung transplantation, as three main technologies for the treatment of PH, have been well-promoted in China in recent years. We observed that BPA could be performed in 68.19% ( $n = 30$ ) of hospitals. The high popularity of BPA may be related to its minimally invasive and good maneuverability. PEA and lung transplantation are required higher technical demands, so only 47.73% ( $n = 21$ ) and 43.18% ( $n = 19$ ) of hospitals can perform them, respectively. Besides, 20.45% ( $n = 9$ ) of hospitals could not be able to perform any of the above-mentioned operations. There is a close relationship between the surgical amounts and the success rates of these three technologies above.

High-volume centers have more experience to ensure medical quality and reduce medical costs.<sup>11</sup> However, in the present study, we found that the number of surgeries was still low, only 8 hospitals (19.05%) could perform more than 50 cases per year and 9 hospitals (47.37%) could perform more than 10 cases of lung transplantation per year. These results demonstrated a significant gap between Chinese tertiary hospitals and international PH centers,<sup>12</sup> and we still have a lot of work to do in treatment-related technology promotion in China.

This study has several limitations. First, the sample size of our study was small, which could result in limitation of representativeness of the results. However, considering the limited number of regional centers of pulmonary vascular diseases in China, the findings of our study still reflect the current problems and status of the management of PH in China. Second, relying on respiratory-related societies and organizations to conduct surveys may indeed lead to some data biases due to different professional backgrounds.

Our study preliminarily reveals the current status of diagnosis and treatment of PH in Chinese tertiary hospitals: the majority of Chinese tertiary hospitals were

well equipped with the corresponding personnel, examinations and medicines related to PH, but the standardization and specialization of the management of PH need to be strengthened. In China's medical security system, combined with the regional socioeconomic characteristics, the standardized clinical practice of PH diagnosis and treatment needs to be further strengthened, and the drugs and treatment techniques should be further promoted, which ultimately lead to the improvement of the PH management system in China.

#### AUTHOR CONTRIBUTIONS

Meng Zhang, Wanmu Xie, Zhenguo Zhai, and Jun Wan designed the survey. Xueran Guo, Ao Yin, and Jiafei Peng collated the survey responses. Meng Zhang, Jun Wan, Yao Xiao, Wei Guo, Yan Wang, Wenmei Zhang, and Shengchen Duan contributed substantially to the data analysis and interpretation. Meng Zhang wrote the first draft. QianGao, Shuai Zhang, and Yunxia Zhang contributed to the writing and review of the manuscript. All authors critically reviewed the final manuscript and provided final approval for manuscript submission.

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#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

#### ETHICS STATEMENT

Our study was designed to evaluate the diagnosis and treatment status of PH in China by surveying physicians in tertiary hospitals, it did not involve patient ethic issues.

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