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ORIGINAL RESEARCH

The Anesthesiologists' Perception of Malignant Hyperthermia and Availability of Dantrolene in China: A Cross-Sectional Survey

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Background: Malignant hyperthermia (MH) is a hypermetabolic syndrome with high mortality rates. Early detection and prompt intravenous administration of dantrolene are crucial for effective management of MH. However, there is currently a lack of comprehensive nationwide surveys on the availability of dantrolene and anesthesiologists' understanding of MH in China.

Methods: A nationwide survey was conducted between January 2022 and June 2022. Online questionnaires on the cognition of MH among anesthesiologists in China were sent through social platforms to anesthesiologists in mainland China. Data regarding participants' perception of MH-related knowledge, availability of domestic dantrolene, and reported MH cases were collected in this study.

Results: Responses were collected from a total of 11,354 anesthesiologists representing 31 provinces across the Chinese mainland. Among the 11 scoring questions, the highest accuracy rates were observed for the question regarding therapeutic drugs for MH (99.3%) and the characteristics of MH (98.0%). Conversely, the question pertaining to the earliest clinical signs of MH had the lowest accuracy rate (23.5%). Significant variations were observed in the scores among different professional titles (P=0.003), academic degree (P<0.001), hospital classification (P<0.001), and urban hierarchy (P<0.001). Of the respondents, 919 (8.1%) anesthesiologists reported dantrolene availability in their hospitals, and 631 (5.6%) indicated unclear. A total of 136 hospitals in this survey reported at least one previous case of MH.

Conclusion: Mainland China faces challenges such as insufficient experience in diagnosing and treating MH, as well as difficulty in obtaining dantrolene. To improve the public awareness of MH, it is imperative to establish and promote a refined MH training system. Additionally, a streamlined and rapid dantrolene linkage emergency system should be implemented to ensure prompt access to the drug.

Keywords: malignant hyperthermia, dantrolene, China, anesthesiologists, survey

Introduction

Malignant hyperthermia (MH) is a hypermetabolic syndrome mainly inherited in autosomal dominant way. It often occurs after exposure to volatile anesthetics and/or depolarized muscle relaxant succinylcholine, and rarely by stress and heat. The estimated incidence of MH varies between 1/10,000 and 1/250,000 anesthetic procedures.[1–3] With an increasing understanding of MH and introduction of intravenous dantrolene in 1979, the mortality rates has decreased from 80.0% to 1.4% in developed countries.[4]

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The mortality rates associated with MH in China was reported as high as 73.5% in the early 21st century.[5] A retrospective analysis of the suspected MH patients from 2015 to 2020 reported a mortality rate of 53.4%.[6] Lack of awareness concerning the availability and accessibility of the orphan drug dantrolene was considered to attribute to the high mortality rates with MH. Intravenous dantrolene was not available in mainland China until Oct 2020, however, the current reserve of domestic dantrolene is not clear. Lack of awareness among anesthesiologists and patients makes it difficult to identify susceptible individuals before the surgery, detect early signs of MH, and provide prompt treatment. To solve these problems, the expert consensus on the prevention and treatment of MH was published by the Chinese Society of Anesthesiologists (CSA) in 2018 and updated in 2020.[7] However, the cognition of MH among anesthesiologists and mortality still varies across different regions.

This study aimed to evaluate the anesthesiologists' perception of MH and the availability of domestic dantrolene in mainland China through online questionnaires. Based on these findings, targeted strategies are able to be proposed to effectively reduce MH mortality.

Materials and Methods

Study Design and Participants

The nationwide survey was conducted between January 2022 and June 2022. All certified practicing anesthesiologists in Chinese mainland were eligible for this survey. The study was approved by the Medical Science Research Ethics Committee of Peking University Third Hospital (approval No. 2021499). This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Participants were recruited via national anesthesiologists' organizations. CSA, China International Exchange and Promotive Association for Medical and Health Care (CPAM) and Chinese Association of Anesthesiologists (CAA), as three national anesthesiology specialty societies and organizations, distributed the link to the online survey through internal social media groups. It was emphasized before the survey that participation was voluntary and anonymous. Written informed consent was obtained from all the participants before the survey.

Survey Questionnaire Design

The survey questionnaire was developed based on previous studies[7] by three of the investigators (JCW, JZ and ZQL). The questionnaire consisted of 23 items, involving three domains related to MH: demographic information about the participant's practice (8 items), general perception of diagnosis and treatment of MH (11 items), access to MH related knowledge, availability of dantrolene sodium, and the incidence of MH in the hospital of participants (4 items). Regarding the participants' perception of MH, each correct answer was awarded 1 point, while wrong answers were awarded 0 points. The maximum score for the perception section was 11 points.

The survey was piloted to 20 anesthesiologists, and the questionnaire was revised according to the feedback. The complete questionnaire is available in Supplementary Material A.

Definitions and Explanations

In Chinese mainland, public hospitals are classified into 3 tiers (ie, tiers 1, 2, and 3). The higher the tier, the better the hospital. Tier 3 hospitals are top-level general hospitals with a bed capacity exceeding 500. Tier 2 hospitals are medium-sized hospitals with 100–500 beds. Tier 1 hospitals are classified as hospitals in rural areas or community hospitals. The ranking of anesthesiologists includes junior (medical assistant, resident), intermediate (attending physician), deputy senior (associate chief physician), and senior (chief physician), which are different from rankings used in Europe and America. The upgrading of a physician's ranking needs to be evaluated according to the practice level, clinical work time, academic achievements, and educational background. Chinese mainland consists of 31 provinces, 3 autonomous regions, and 4 municipalities. The municipalities include Beijing, Tianjin, Shanghai, Chongqing. The provincial capital cities include: Shijiazhuang, Taiyuan, Hohhot, Shenyang, Changchun, Harbin, Nanjing, Hangzhou, Hefei, Fuzhou, Nanchang, Jinan, Zhengzhou, Wuhan, Changsha, Guangzhou, Nanning, Haikou, Chengdu, Guiyang, Kunming, Lahsa, Xi'an, Lanzhou, Xining, Yinchuan, Urumqi. Provincial capital cities and municipalities often have a larger urban area and a larger residential population, playing an important role in politics, economy, culture, and other aspects.

Statistical Analysis

All statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL). Continuous variables were expressed as mean (SD) or median [interquartile range (IQR)], and analyzed with Student's *t*-test or Mann–Whitney *U*-test as appropriate. Categorical data were presented as numbers (percentages), and compared using the chi-square test or Fisher exact test. $P < 0.05$ was considered statistically significant.

Results

Survey Responses and Demographics

A total of 11,354 anesthesiologists across 31 provinces in mainland China participated in our survey. Supplementary material B illustrates the distribution of anesthesiologists across provinces. A response rate cannot be calculated because the precise number of anesthesiologists who received the invitation was unknown. Forty-two percent (4,770/11,354) of the participants provided the exact name of the medical center, and at least 1,833 hospitals participated in the questionnaire. At present, there are approximately 100,000 anesthesiologists in mainland China, therefore more than one tenth of all the anesthesiologists participated in the study. Demographic information about the participants' practice is listed in Table 1. None of the participants practiced in private practice setting.

Participants' Perception of MH Related Knowledge

Among the 11 scoring questions, the correct rates of therapeutic drugs for MH (99.3%) and the characteristics of MH (98.0%) were the highest. The correct rate for the earliest clinical signs of MH was the lowest (23.5%), with 69.1% of anesthesiologists believing that the rapid elevation of body temperature was the initial symptom. The correct rates for classification of MH (53.2%), the MH susceptible population (57.2%), the MH susceptible screening methods (69.4%), and the precipitating factors of MH

Table 1 Demographic Information of the Responding Anesthesiologists

Characteristics	N=11,354
Professional title, n (%)	
Residents	3,026 (26.6)
Attending physicians	4,391 (38.7)
Associate chief physicians	2,800 (24.7)
Chief physicians	1,137 (10.0)
Academic degree, n (%)	
Other's degree	780 (6.9)
Bachelor's degree	7,972 (70.2)
Master's degree	2,234 (19.7)
Doctorate degree	368 (3.2)
Working years	
1–20	7,815 (68.8)
>20	3,539 (31.2)
Hospital classification, n (%)	
Tier 3	7,175 (63.2)
Tier 2	4,179 (36.8)
Tier 1	0 (0)
Urban hierarchy, n (%)	
Municipality	1,877 (16.5)
Provincial capital city	2,464 (21.7)
Other city	7,013 (61.8)

Notes: Tier 3: Tier 3 hospitals are top-level general hospitals with a bed capacity exceeding 500; Tier 2: Tier 2 hospitals are medium-sized hospitals with 100–500 beds; Tier 1: Tier 1 hospitals are classified as hospitals in rural areas or community hospitals.

(64.5%) were higher than 50%. On the other hand, the correct rates for the inheritance mode of MH (45.0%), the optimal timing for dantrolene administration (48.9%), and the preparation method of domestic dantrolene (45.9%) were less than 50% (Figure 1).

According to our survey, there is a widespread lack of knowledge related to MH across China. Anesthesiologists who participated in the national questionnaire had a median score of 6 (5,8), with the accuracy rate is 54.5%. Factors associated with scores are displayed in Table 2. There are significant differences in scores among participants with different professional titles ($P = 0.003$). Specifically, the scores of chief physicians were significantly higher than those of associate chief physicians ($P = 0.011$) and attending physicians ($P = 0.002$). There were also significant differences in scores among participants with different academic degrees ($P < 0.001$). The scores of those with doctorate degrees were significantly higher than those with bachelor's degree ($P < 0.001$) and others ($P < 0.001$). However, there was no significant difference in scores among participants with different working years ($P = 0.913$). Additionally, the scores of anesthesiologists in tier 3 hospitals were significantly higher than those in tier 2 ($P < 0.001$, Figure 2).

All cities that participated in the survey were classified into municipalities, provincial capital cities, and others. The scores of participants from different regions varied significantly ($P < 0.001$). Specifically, the scores of provincial capital cities were significantly lower than those of municipalities ($P < 0.001$), while higher than those of normal cities ($P < 0.001$, Figure 2).

Access to MH-Related Knowledge

Professional books were the most frequently used approach of the anesthesiologists who participated in the survey for acquiring knowledge related to MH (84.1%), followed by the Internet (57.5%), literature (55.7%), lectures (67.7%), and news reports (13.3%). It is noteworthy that 0.6% of anesthesiologists have never followed up to closely on this area (Figure 3).

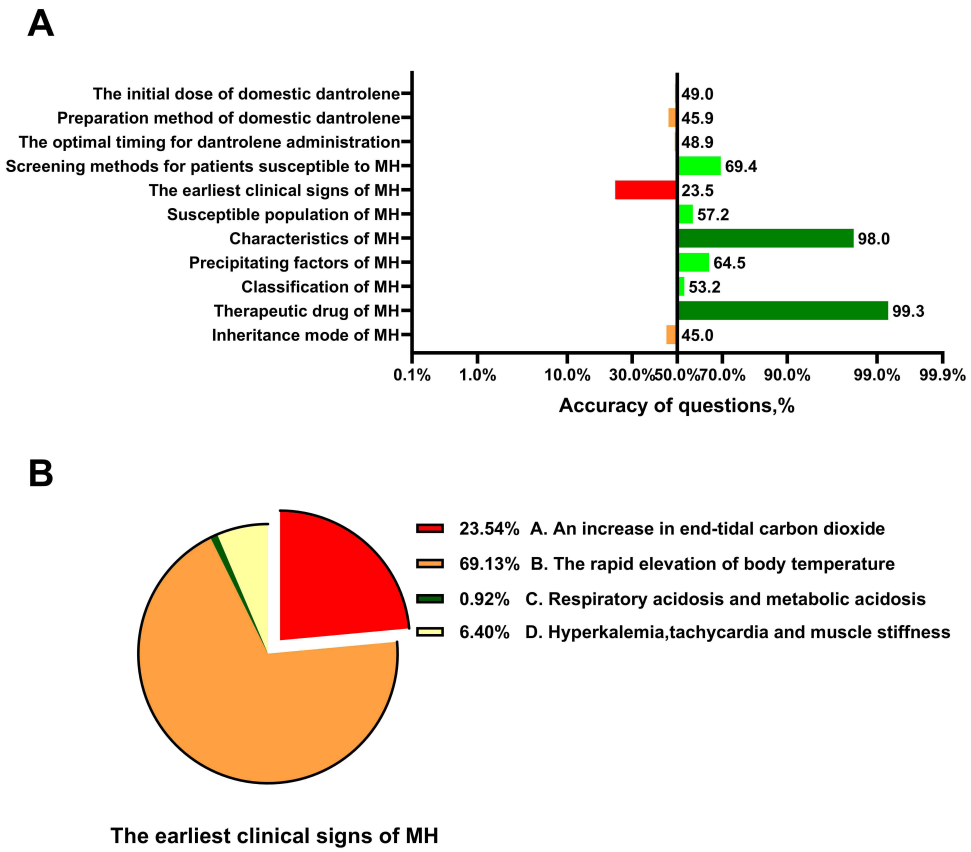

Figure 1 Participants' perception of MH related knowledge.
Notes: (**A**) Correct rates of answers for each question; (**B**) The earliest clinical signs of MH. The pie chart represents the proportion of anesthesiologists giving the respective response.
Abbreviation: MH, malignant hyperthermia.

Table 2 Difference of Scores Among Population with Different Characteristics

Characteristics	Score, median [IQR]	Z/H	*P*
Professional title		12.773	0.003
Resident	6 (5,8)		
Attending doctor	6 (5,8)		
Associate chief physician	6 (5,8)		
Chief physician	7 (5,8)		
Academic degree		49.712	<0.001
Other's degree	6 (4,8)		
Bachelor's degree	6 (5,8)		
Master's degree	7 (5,8)		
Doctorate degree	7 (5,8)		
Working years		−0.109	0.913
1–20	6 (5,8)		
>20	6 (5,8)		
Hospital classification		−8.121	<0.001
Tier 2	6 (5,8)		
Tier 3	6 (5,8)		
Urban hierarchy		91.912	<0.001
Municipality	7 (5,9)		
Provincial capital city	6 (5,8)		
Normal city	6 (5,8)		

Notes: Tier 3: Tier 3 hospitals are top-level general hospitals with a bed capacity exceeding 500; Tier 2: Tier 2 hospitals are medium-sized hospitals with 100–500 beds. Professional title: the scores of chief physicians were significantly higher than those of associate chief physicians ($P = 0.011$), and attending physicians ($P = 0.002$). Academic degree: the scores of doctorate degree were significantly higher than bachelor's degree ($P < 0.001$) and others ($P < 0.001$); the scores of master's degree were significantly higher than bachelor's degree ($P < 0.001$) and others ($P < 0.001$). Urban hierarchy: the scores of provincial capital cities were significantly lower than those of municipalities ($P < 0.001$), while higher than those of normal cities ($P < 0.001$).
Abbreviations: Z: Mann–Whitney *U*-test value; H: Kruskal–Wallis test value; *P*, significance value.

Availability of Domestic Dantrolene in Mainland China

Among the anesthesiologists who participated in the questionnaire, 4,771 (42.0%) filled in the names of the hospitals. After removing duplicate values, 1,833 hospitals were included in the analysis, out of which only 52 (2.8%) had domestic dantrolene. Based on urban hierarchy classification, the proportion of hospitals with domestic dantrolene was significantly higher in municipalities (8.9%) than in provincial capital cities (5.4%) and others (1.4%). The differences across the regions were statistically significant based on regional distribution classification (Table 3). The proportion of hospitals with domestic dantrolene was highest in northern mainland China (6.2%). None of the hospitals in northwest of Chinese mainland has the availability of domestic dantrolene. We have also produced a map to illustrate the availability of domestic dantrolene in mainland China (Figure 4).

Distribution of Reported MH Cases in Mainland China

A total of 136 hospitals in this survey reported at least one previous case of MH. These hospitals are distributed in 27 provinces. Detailed information on the specific distribution and the number of hospitals with reported cases are shown in Figure 5.

Discussion

This national survey represents the largest comprehensive investigation conducted on the status of MH in China. Currently, there are approximately 100,000 anesthesiologists in mainland China, of which 11,354 (11.35%) from 31

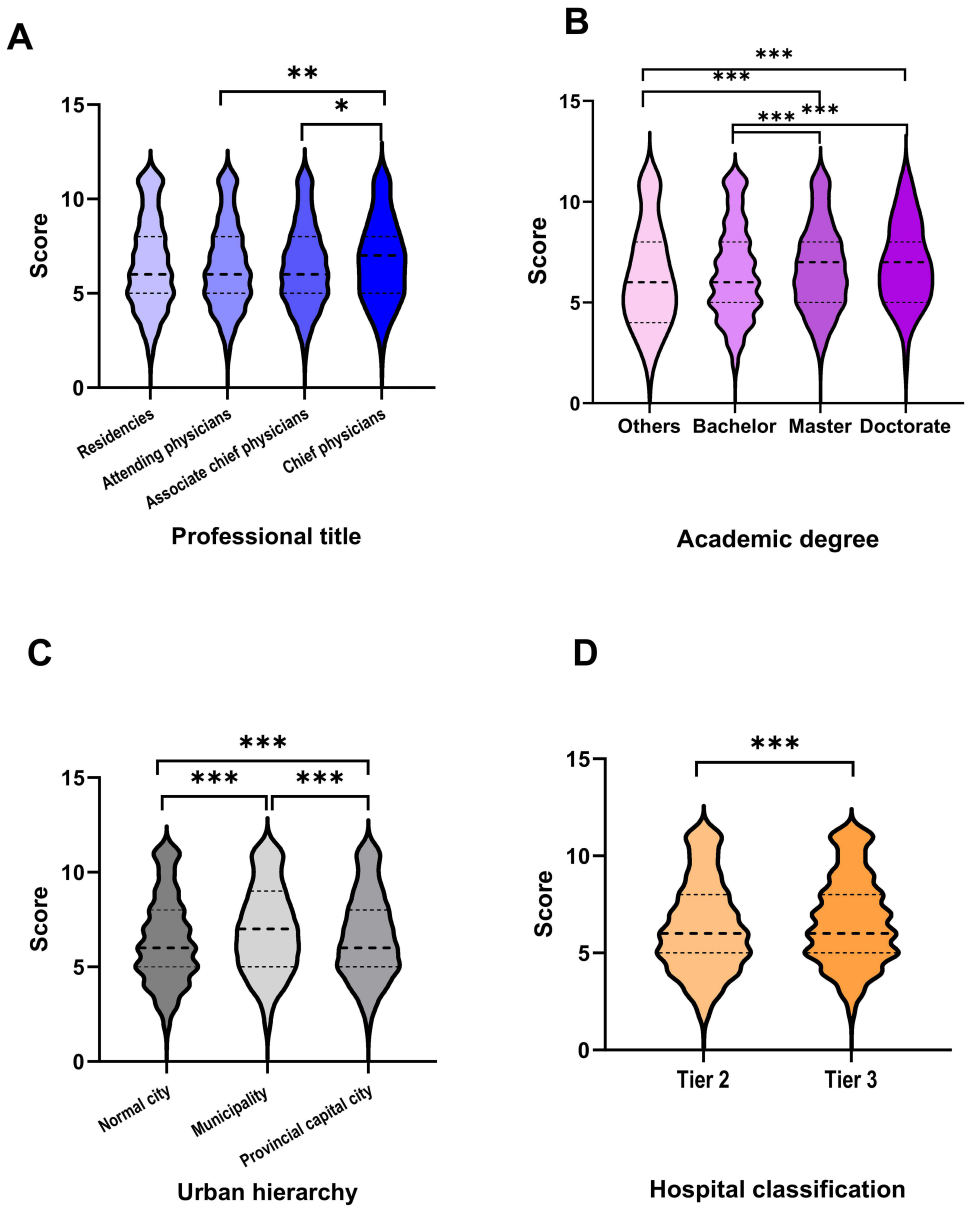

Figure 2 Differences of scores among population with different characteristics.
Notes: (**A**) Scores for different professional titles; (**B**) Scores for different academic degree; (**C**) Scores for different urban hierarchy; (**D**) Scores for different hospital classification. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
Abbreviation: *P*, significance value.

provinces completed the web-based questionnaire. The results showed a significant gap among anesthesiologists regarding knowledge and practices of MH. The level of MH knowledge varied based on professional titles and regions. Moreover, the availability of dantrolene was found to be inconsistent throughout mainland China. It is worth noting that possessing a good knowledge does not necessarily guarantee the availability of dantrolene.

A previous study completed by a total of 1,357 valid questionnaires was conducted by the West China Hospital of Sichuan University in 2021, providing valuable insights into the regional landscape of the cognitive evaluations and difficulties associated in dealing with MH among Chinese anesthesiologists in China, with 41.0% of participants representing the Sichuan Province.[8] In contrast, the extensive participation of anesthesiologists in this study from diverse provinces enhances the overall representation and significance of the findings. This study has shed light on the primary challenges confronted by anesthesiologists all around China, namely the difficulties in acquiring dantrolene and the insufficient experience and knowledge in managing MH.

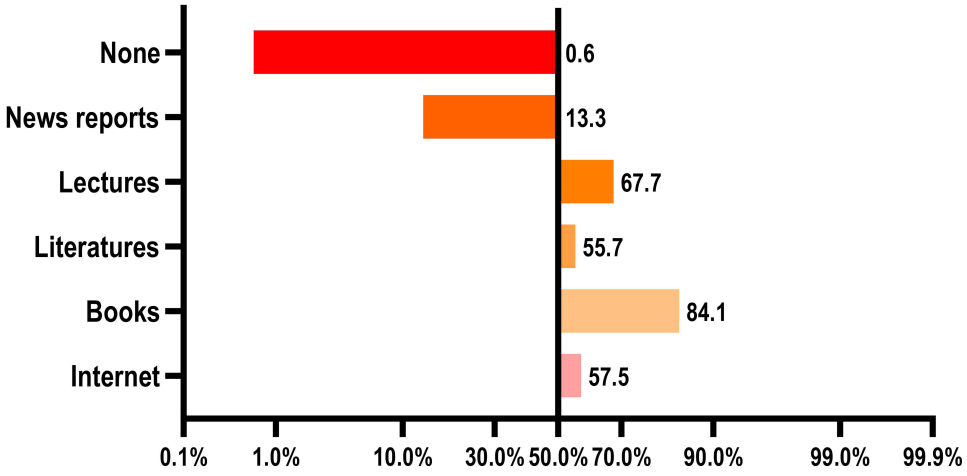

Figure 3 Access to knowledge of MH.
Notes: None, never obtained relevant knowledge of MH.
Abbreviation: MH, malignant hyperthermia.

The mortality rate of MH in China was reported to be 45.7%.[9] The clinical manifestations of MH can exhibit significant variabilities, and the failure to promptly identify this condition remains a key factor contributing to the high mortality rate.[10] In this nationwide survey, we observed that only 23.5% of anesthesiologists accurately recognized an increse in end-tidal carbon dioxide as the initial symptom of MH, while a significant majority (69.1%) believed that rapid elevation of body temperature serving as the first indication. These findings underscore the concerning fact that a majority of anesthesiologists were unable to promptly recognize MH and maintain a high level of vigilance. This knowledge gap can potentially result in delayed administration of dantrolene, compromising the timely and effective treatment of MH. Hence, it is crucial to implement multidisciplinary team training approaches that encompass theoretical education and simulated role-playing scenarios. These initiatives would offer anesthesiologists opportunities to enhance their teamwork skills and multidisciplinary communication, particularly in remote areas where dantrolene may not be readily accessible. In addition, to our knowledge, Clinical Grading Scale (GCS) is used for severity assessment in most newly diagnosed MH cases in China. As we all know, the most accurate diagnostic methods for MH are the Caffeine and Halothane Contracture Test (CHCT) and the Caffeine Contracture Test (IVCT). As an important MH rescue center

Table 3 Availability of Dantrolene in Mainland China

Characteristics	Number of Hospitals(n=52)	*P*
Urban hierarchy, n (%)		<0.001
Municipality	13 (25.0)	
Provincial capital city	21 (40.4)	
Normal city	18 (34.6)	
Regional distribution, n (%)		<0.001
North China	12 (23.1)	
Central China	3 (5.8)	
South China	10 (19.2)	
East China	13 (25.0)	
Southwest China	13 (25.0)	
Northwest China	0 (0)	
Northeast China	1 (1.9)	

Notes: A total of 52 hospitals across the country have domestic dantrolene in availability. *P*, significance value.

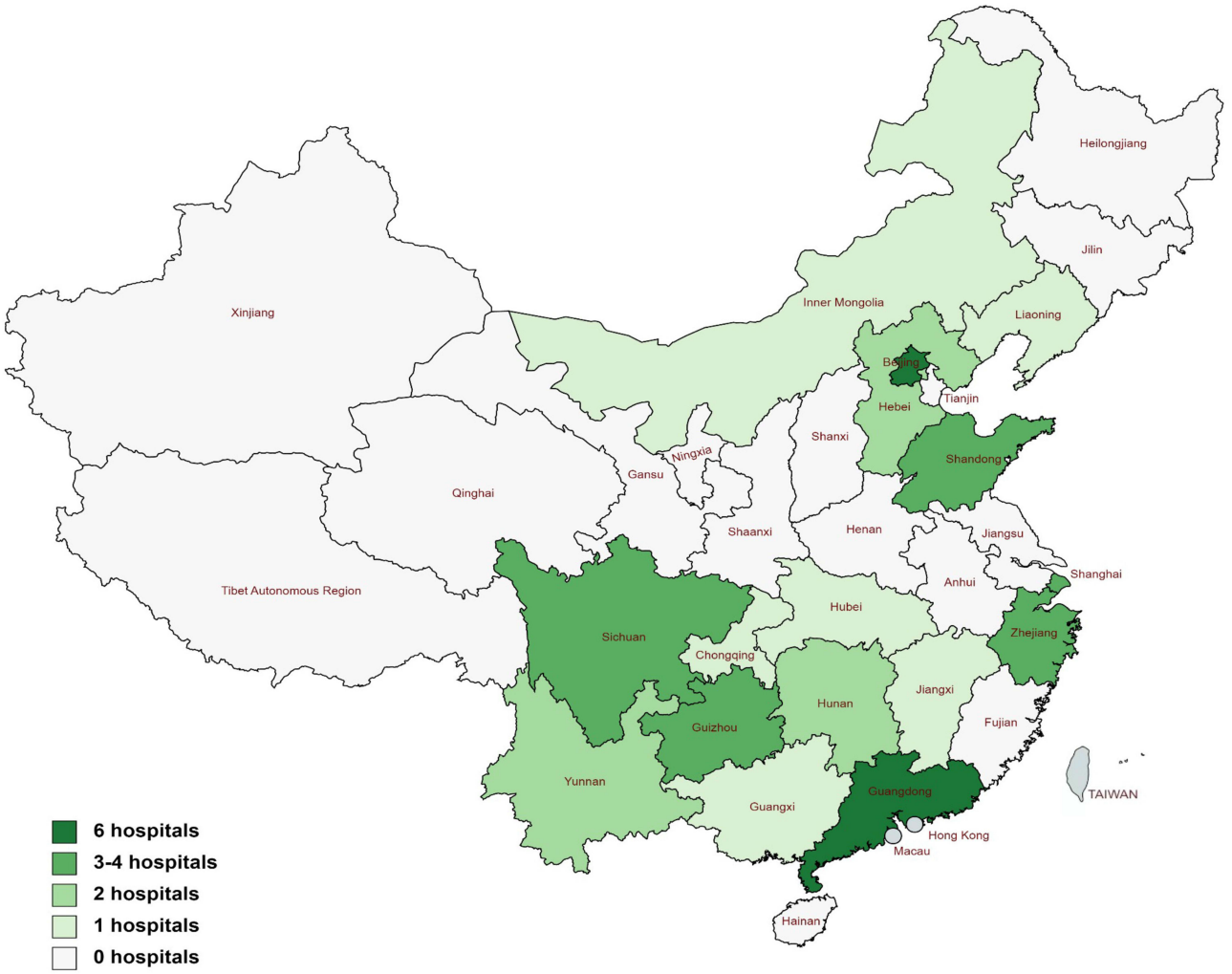

Figure 4 Availability of domestic dantrolene in mainland China.
Notes: The map illustrates the distribution of hospitals with available dantrolene across provinces, with darker shades indicating a higher number of hospitals possessing dantrolene. The legend in the lower left corner displays the numbers of hospitals with dantrolene available.

located in North China, our institution has consistently exerted diligent efforts. We have successfully instituted a CHCT experimental framework. We anticipate making further substantial contributions to diagnostic endeavors in the country.

In this survey, chief physicians showed a better understanding of MH compared to other professional titles. Higher education levels (doctorate or master's degree) correlate with higher levels of MH knowledge. Anesthesiologists in tier 3 hospitals exhibit higher knowledge than those in tier 2 and tier 1 due to specialized training and clinical experience. Anesthesiologists in municipalities and provincial capital cities demonstrate higher MH knowledge, likely due to the socioeconomic inequality in health,[11] which allows them to have higher educational background and access to more resources and training opportunities. These results highlight the urgent need for a comprehensive MH training system, like the cardiopulmonary resuscitation training model developed by the American Heart Association. A dedicated MH website should be created, providing guidelines, knowledge, simulated scenario exercises, theoretical and simulated assessments. Medical staff in the department of anesthesiology can receive training through the system and obtain a certificate upon successful completion.

Dantrolene is currently the only specific drug for the treatment of MH, which should be used as soon as possible.[12] However, our survey results revealed that more than half of anesthesiologists lack knowledge regarding the optimal timing and preparation method of domestic dantrolene. This shows that in the event of MH, a significant number of anesthesiologists may be unable to use dantrolene in a timely and correct manner, potentially resulting in failed rescue

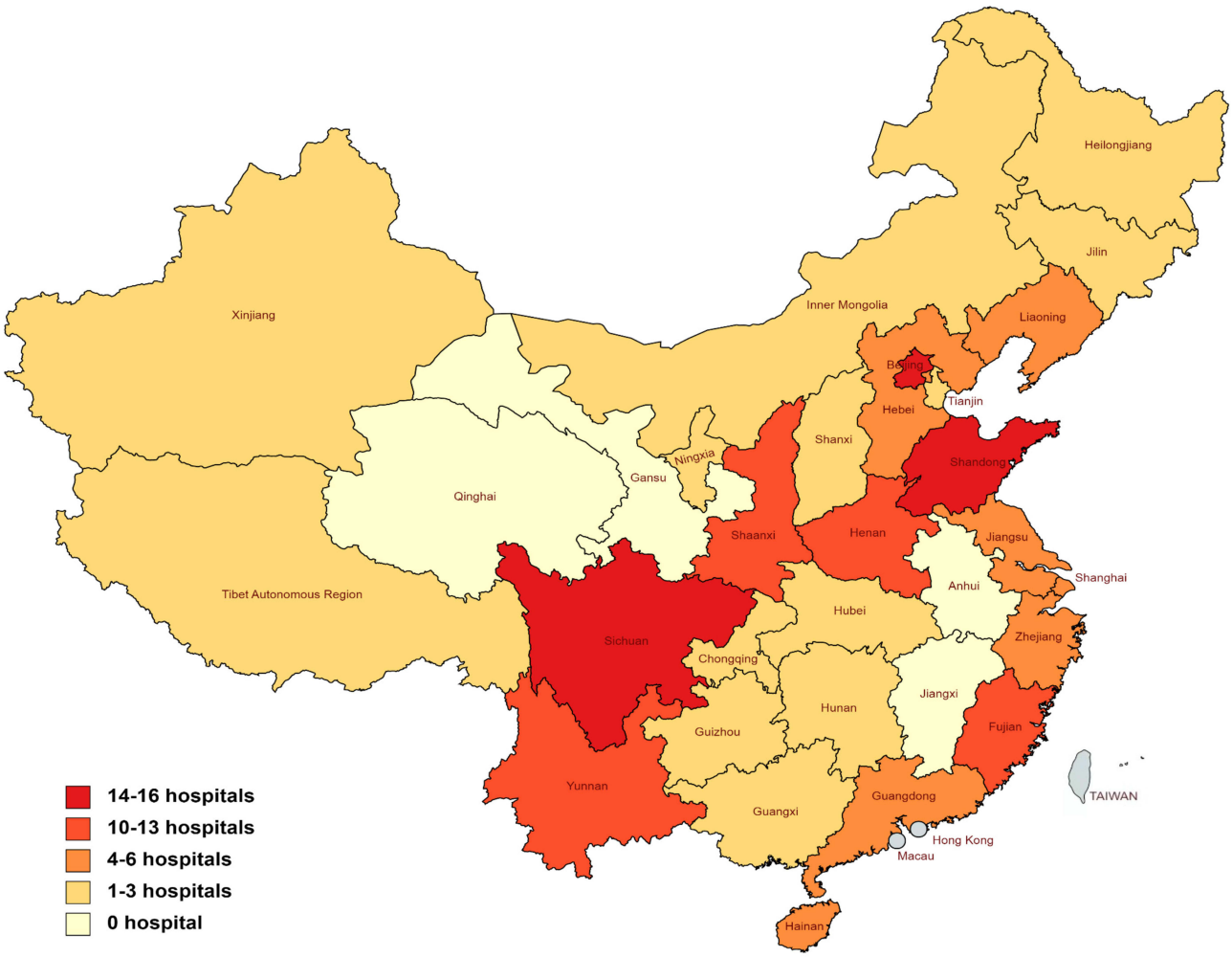

Figure 5 Distribution of hospitals reporting MH cases.
Notes: The map illustrates the distribution of hospitals reporting MH cases in each province. Darker color represents a higher number of hospitals with MH cases. The legend in the lower left corner displays the numbers of hospitals with cases reported.
Abbreviation: MH, malignant hyperthermia.

attempts. In the absence of dantrolene, CSA recommends symptomatic treatment and continuous renal replacement therapy (CRRT) to protect important organ functions. Fortunately, with years of relentless efforts, domestic dantrolene for injection (Livzon Pharmaceutical Group Co., Ltd, Zhuhai, China) has obtained the approval by the National Medical Products Administration (NMPA) in October 2020[13] and has since then been implemented in clinical practice. While MH associations in many countries recommend that hospitals using inhaled anesthetics and succinylcholine should stock dantrolene, the stock model of dantrolene has been a subject of debate in China due to the rarity of MH, concerns about drug wastage, and a lack of cost-benefit analysis regarding dantrolene reserves.[14,15]

The findings of this study showed that hospitals equipped with domestic dantrolene are primarily concentrated in municipalities and provincial capital cities. Surprisingly, there was no significant correlation between the knowledge level of anesthesiologists and the availability of domestic dantrolene. This indicates that enhancing MH knowledge among anesthesiologists alone is insufficient to promote the widespread stocking of dantrolene. Multiple factors may have influence on dantrolene availability, such as socioeconomic status, government policies, and the occurrence of MH cases within a particular region. CSA has been actively promoting the development and production of domestic dantrolene for many years, especially in the popularization of relevant knowledge of the drug. To address these challenges, it is imperative to establish an adequate national pharmaceutical stockpile system tailored to China's unique

circumstances. Take the "fire hydrant" model proposed by the Beijing Center of Quality Control and Improvement on Clinical Anesthesia for MH rescue for example: if the MH case ("fire") occurred in a medical institution, the medical center provide the initial dose of dantrolene ("fire hydrant"), and the maintaining dosage were urgently delivered by provincial emergency drug reserve institution ("fire truck"). The utilization of this model has demonstrated success, establishing it as an efficacious and efficient option. We recommend its consideration for adoption by policymakers. This collaborative emergency system can be extended nationwide while encouraging hospitals with appropriate resources to maintain the dantrolene reserves.

The survey results indicated that 136 hospitals across 27 provinces in China had reported the cases of MH. The number of MH case in China from 1985 to 2020 was reported as 92 cases in Gong's study.[9] A total of 58 suspected MH cases occurred from 2015 to 2020 were reported in a retrospective study.[6] It is worth noting that these figures likely underestimate the actual incidence of MH. Therefore, a nationwide MH registration institution should be established to standardize the management of MH cases, collect susceptibility information, and compile genetic data.

The study has a few limitations. First of all, although anesthesiologists from 31 provinces participated in this survey, not all primary hospitals were included. However, from 2015 to 2017, there were approximately 46 million general anesthesia surgeries in mainland China every year, of which 80% occurred in hospitals at or above tier 2, while tier 1 or lower hospitals mainly focus on chronic disease care.[16] Another limitation to the present study is the absence of data about monitoring equipment, such as intraoperative temperature monitoring and carbon dioxide monitoring, which should be addressed in future investigations. Finally, this survey focused on local and national challenges, which varies across low-, middle-, and high-income countries around the world. Each nation must internally address such circumstances on a case-by-case basis.

Conclusions

The current diagnosis and treatment of MH among Chinese anesthesiologists require improvement. It is crucial to establish and promote a comprehensive MH training system to strengthen the training of all anesthesiologists. The current dantrolene reserves across various regions of the country are insufficient. Implementing an efficient dantrolene linkage emergency system across the country is vital for timely acquisition and administration of dantrolene during MH incidents.

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Disclosure

The author(s) report no conflicts of interest in this work.

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