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Current state of care for the elderly in China in the context of an aging population

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SUMMARY The aim of the current study was to review the current state and characteristics of the elderly population in China in the context of aging, difficulties and challenges faced by older people, and efforts of the current Chinese Government in this area. The process of population aging in China began to accelerate in the late 1970s and has continued to increase at a rate of about 3.2% per year since then. This process took more than 45 years in developed countries, while it took only about 27 years in China, and aging may continue to increase for a long time. China is now moving toward a superannuated society due to declining fertility rates and increasing life expectancy. There is a great need for care due to the high disease burden among older people. However, more than 1 million "families have lost their only child", and this number is increasing annually by about 76,000; moreover, there are a large number of "deficient families [with an injured family member]" in China. These families face greater difficulties due to aging and need to rely on society for more support given the lack of care provided by their children or spouses. The current study has focused on improving the quality of life of older people, helping them achieve healthy aging, and to assist the country in further providing care for the elderly.

Keywords integrated elderly and medical care, care for the elderly, elderly care consultant system, Internet + care for the elderly, community-embedded care for the elderly, population aging

1. Introduction

At present, China has the largest elderly population in the world (*1*).According to the results of the seventh national census in 2020, people ages 60 and older accounted for 18.7 % of China's total population, up to 264 million people, while those age 65 and older accounted for 13.5 %, up to 190 million people (*2*). Population aging has become a significant trend in China's social development, and the degree of population aging in China has further intensified. In conjunction with accelerating population aging, the issue of care for the elderly in China has increasingly drawn the high attention of the government and the community.

In terms of the course of one's life, the health status of older adults decreases with age. Among China's huge elderly population, a relatively high proportion of the elderly have chronic diseases or other geriatric conditions, and a considerable portion of the elderly are in poor health. Data from the 2020 China Health Statistics Yearbook (*3*) indicate that in 2019, elderly people over 60 years of age accounted for 40.01% of patients discharged from hospitals. This indicates that the health status of the elderly in China is poor. The massive size of the elderly population and the poor health of the elderly have led to a huge demand for health and elderly care, and the demand is multi-faceted and varied. This has led to a series of problems and great challenges in terms of the development of health and nursing care for the elderly.

China is a vast country, and the problem of unbalanced socio-economic development in different regions is relatively pressing. China is considered a developing country, but its GDP exceeded the 15.87 trillion US dollars mark in 2020 and the country become the world's second largest economy (*4*). Nonetheless, China's per capita income is still low, and China's aging population is more serious and complicated than that of other developed countries and regions in the world. Vigorous development of care for healthy elderly is a

complex systemic project that requires the joint efforts of the entire society to create a social environment conducive to the healthy aging of the elderly, to improve the quality of life of the elderly population, and to help the elderly enjoy long and healthy lives. The aims of the current work were to analyze the problems and challenges faced by China's care for the elderly in the context of aging and to summarize the Chinese Government's current efforts to provide care for the elderly.

2. Status and characteristics of the aging population in China

2.1. A large and rapidly growing aging population

The process of population aging in China began to accelerate in the late 1970s and has continued to increase at a rate of about 3.2% per year since then (*5*). This process took more than 45 years in developed countries, while it took only about 27 years in China, and aging may continue to increase for a long time (*6*). China is now moving toward a superannuated population due to declining fertility rates and increasing life expectancy. According to the National Bureau of Statistics (*7*), the natural population growth rate in China dropped from 25.9% to 1.45% between 2013 and 2020, while the number of people over the age of 65 increased by 58 million, accounting for a 6.8% increase. The dependency ratio of the elderly population increased from 13.1% to 19.7%. By 2020, the number of people ages 65 and older in China reached 191 million, accounting for 13.5% of the population. The extent of aging has reached 18.7%, resulting in a moderately aging population (Table 1) (*8*). According to the Report of Forecasts of Trends in Population Aging in China (*9*), from 2021 to 2050, China will enter a phase of accelerated aging. In addition, the proportion of the elderly population age 65 and older will reach 18.44% in 2030, 26.22% in 2040, and 29.80% in 2050. From 2051 to 2100, China is expected to have stable and increased aging. In 2051, the size of the elderly population in China will reach a peak of 437 million, and its size will stabilize at 300-400 million. Around 2030, the dependency ratio of the elderly population in China is expected to reach about 25%, and around 2045, it will exceed the ratio in developed countries. Moreover, it will be higher than the world average for a long time, and the aging population will be a heavy burden on society.

2.2. Rapid aging of the population in China

The population ages 60-69 is called the younger elderly population, that ages 70-79 is called the moderately elderly population, and that ages 80 years and older is called the older elderly population (*10*). With improvements in living standards and medical technology, average life expectancy is increasing. The average life expectancy was 69.03 years in 1990, 71.73 years in 2000, and 75.01 years in 2010; average life expectancy is expected to reach nearly 80 years in 2050 (*11*). As the average life expectancy increases, the age structure of the elderly population will expand at the top, the elderly at the top of the structure will age, and advanced aging of the population will become more evident. The number of older elderly in China was about 7.766 million in 1990 and 20.989 million in 2010, accounting for about 11.8% of the total elderly population. By 2020, the number of senior citizens reached 35 million, accounting for about 14.0% of the total elderly population (Figure 1A) (*8*). The elderly population ages 80 and older is forecast to be 54.48 million in 2030 and 133 million in 2050, accounting for 26.2% of the world's elderly population (*12*). The growth rate of the older elderly population is much higher than the growth rate of the elderly population overall. A large number of older people will more likely live with illnesses and be bedridden. In addition, most of them cannot take care of themselves and need care and attention, requiring a large amount of medical resources per capita.

2.3. Aging trends are reversed in urban and rural areas

China's urbanization is accelerating, with a large number of the young and middle-aged rural labor force migrating to cities. Aging of the rural population is more severe and faster than that of the urban population, and aging is one of the serious problems facing rural

Table 1. Population size, dependence, and natural population growth rate of older*

Year	Population size (billion)	Proportion (%)	Elderly dependency ratio (%)	Natural population growth rate (%)
2013	1.32	9.7	13.1	5.9
2014	1.39	10.1	13.7	6.71
2015	1.45	10.5	14.3	4.93
2016	1.50	10.8	15.0	6.53
2017	1.59	11.4	15.9	5.58
2018	1.67	11.9	16.8	3.78
2019	1.77	12.6	17.8	3.32
2020	1.91	13.5	19.7	1.45

*People ages 65 and older in China (2013-2020) (Data source: *Ref*. (*8*)).

areas (*13*). According to data from the third to sixth national censuses, the rural population over the age of 65 accounted for 5% of the total rural population in 1982, 0.09 percentage points higher than the national average. In 1990, the rural population ages 65 and older accounted for 5.74% of the total rural population, 0.17 percentage points higher than the national average. In 2000, the rural population ages 65 and older accounted for 7.5% of the total rural population, 0.54 percentage points higher than the national average. In 2010, the rural population ages 65 and older accounted for 10.06% of the total rural population, 1.14 percentage points higher than the national average (*14*). Statistics indicate that in 2008, aging in urban areas was 0.13% lower than that in rural areas, and population aging in rural areas reached about 9.79% (*15*). Aging trends are reversed in urban and rural areas, but according to regulations governing China's population development by 2040 those trends will change, and the urban population will be older than the rural population (*9*). The phenomenon of a growing disparity between aging of the urban and rural population is a rarity in the world.

3. Challenges due to current issues with care for the elderly

3.1. The problem of older people living alone and insufficient funds for them

Due to the longstanding "one-child" policy and population migration to big cities, the problem of older people living alone in China has gradually become more pressing (*16*). According to the China Development Research Foundation, the number of older people living alone in China will exceed 30 million in 2025, and it will reach 53.1 million by 2050 (Figure 1B) (*17*). In addition, "families who have lost their only child" in China cannot be ignored. Currently, there are more than 1 million "families who have lost their only child", and that number is increasing annually by about 76,000; in addition there are also a large number of "deficient families [with an injured family member]" in China (*18*). Due to the lack of care provided by their children or spouses, these families face greater difficulties in aging and need to rely on society to get more support during aging.

The process of population aging is relatively faster than economic and social development. Consequently, China is facing the problem of aging. As its population ages, China's GDP per capita is significantly lower than that of the US, Japan, or South Korea (Figure 2). The US had a moderately aging population in 2014, Japan did so in 1995, and South Korea did so in 2018. At those times, the US had a GDP per capita of $51,000, Japan had a GDP per capita of $43,000, and South Korea had a GDP per capita of $33,000 (19). However, China's current GDP per capita is only $12,500 (*20*), which is still

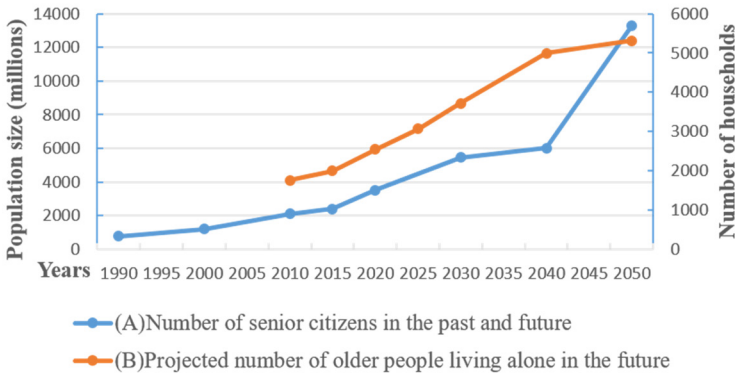

Figure 1.·(A) Number of senior citizens in the past and future. Data source: China. Development Research Foundation. **(B) Projected number of older people living alone in the future.** Data source: China. Development Research Foundation. (Number of households). Data source: National Bureau of Statistics historical census data; projections calculated from the following sources: National Bureau of Statistics of the People's Republic of China. China 2000 Population Census Information [M]. Beijing: China Statistical Publishing 2002.

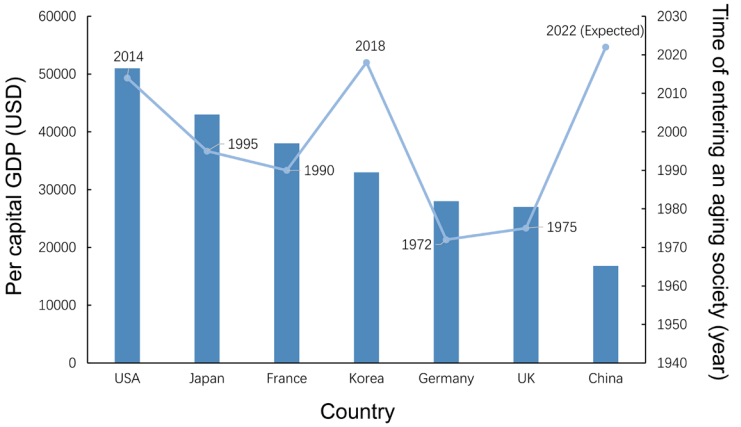

Figure 2. China has a phenomenon of "getting old before getting rich" (USD). Entering an aging population GDP per capita (USD, constant prices). Data source: World Bank, *https://data.wordbank.org.cn*

Table 2. Concomitant chronic diseases among the elderly of different ages in 2010*

Age (years)	Number of patients with chronic disease	1 chronic disease No. (%)	2 chronic illnesses No. (%)	≥ 3 chronic diseases No. (%)
60 - 64	5,160	3,833 (74.28)	1,172 (22.71)	155 (3.01)
65 - 69	3,698	2,636 (71.28)	923 (24.96)	139 (3.76)
70 - 74	2,867	1,988 (69.34)	759 (26.47)	120 (4.19)
75 - 79	1,655	1,183 (71.48)	399 (24.11)	73 (4.41)
≥ 80	936	659 (70.40)	222 (23.72)	55 (5.88)

* Data source: *Ref*. (*29*).

lagging behind that of the US, Japan, and South Korea in the same period, and the problem of "getting old before getting rich" is more serious in China. The shortage of elderly care facilities has always been a major challenge. Elderly care facilities developed significantly under the "12th Five-Year Plan" and "13th Five-Year Plan," (*21*). However, the unbalanced and insufficient configuration of elderly care facilities is still a bottleneck that restricts the development of quality facilities, especially in large- and medium-sized cities and old communities (*22*).

In terms of pension funding, nearly half of China's older people rely on pensions as their main source of livelihood, resulting in an increase in their financial independence. According to Peng *et al*. (*23*), 80.1% of children in China provide intergenerational transfers (including commutation of various types) to their elderly parents. At the national level, the top three main sources of livelihood for older adults with the highest percentages were their own pensions (46.2%), financial support from their children (21.7%), and income from their own labor or work (16.1%) (*24*). Compared to the results of the sixth census in 2010, the proportion of the elderly population in China relying on pension as their main source of income has increased from 24.1% to 46.2%, an increase of about 22 percentage points. Moreover, according to the China Longitudinal Aging Social Survey, 91.25% of the urban elderly population received pensions in 2014, and pensions were the main source of livelihood for 71.93%; although 70.79% of rural older people received pensions, only 17.22% relied on pensions as their main source of livelihood (*24*). However, pension contributions have decreased in amounts and size due to the decline in the working population and a series of corporate tax cuts and fee reductions introduced by the Chinese Government. That said, the population aging combined with increasing life expectancy has led to an increase in the number and frequency of pension payouts. The imbalance between supply and demand has led to a widening gap in the basic government pension in China (*25*).

3.2. A heavy disease burden and greater need for care among older people

The National Assessment Report on Aging and Health in China states that about 33% of the total disease burden in China is attributable to health problems in the elderly population (*26*). The disease burden among older people in China is higher than that in other low-income countries due to the increased per capita burden of chronic diseases.

According to statistics, nearly 80% of older people in urban and rural areas of China suffered from chronic diseases in 2015, and 48.8% of them had two or more chronic diseases at the same time (comorbidities) (*27*). The rate of comorbidities among elderly inpatients was even higher at 91.36%, with 4.68 diseases per capita (*28*). According to a 2010 large-scale survey (*29*), the risk of comorbidity increases with age (Table 2), with the proportion of elderly residents age 80 and older suffering from 3 or more chronic diseases (5.88%) being 1.95 times higher than that of elderly residents ages 60-64 (3.01%). In 2012, nearly 80% of deaths in the Chinese population ages 60 and older were attributable to chronic noncommunicable diseases such as hypertension and diabetes, and the disability rate in the population ages 60 and older was 3.6 times higher than that in the total population (*30*). Concomitant chronic diseases and multiple illness lead to an increase in the number of disabled and semi-disabled older people. The projections (*31*) indicate (Figure 3) that the number of disabled and semi-disabled older people in China reached 76.11 million in 2020 and will increase to 120 million in 2050. There are more than twice as many semi-disabled older people as disabled older people, but the number of disabled older people is increasing faster than the number of semi-disabled older people. Moreover, predictions indicate that there will be 64.63 million semi-disabled older people and 1148 disabled older people in 2030. By 2050, the number of semi-disabled older people ages 80 and older in China will reach about 100 million, with an average annual growth rate of about 3%, and the number of disabled older people will reach 20.72 million, with an average annual growth rate of 3.7%, resulting in a more serious burden of disease and care (*32,33*).

The proportion of older people who need home medical care and professional caregivers continues to increase because of their limited mobility, reduced ability to take care of themselves, and inability to receive timely medical assistance due to multiple diseases. A survey indicated that older people have a greater need for community medical care (16.30%); the greatest needs are

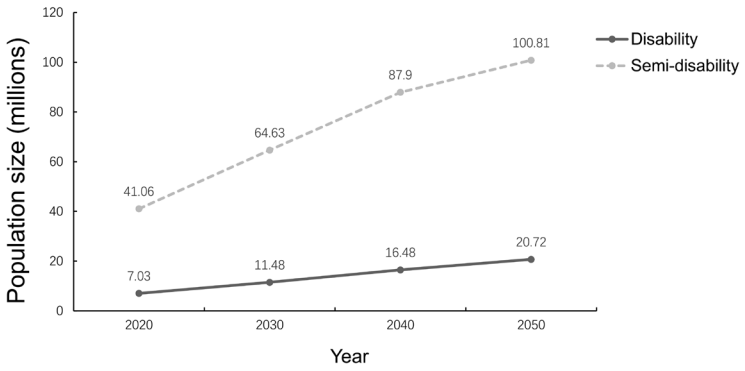

Figure 3. Scale of disabled and semi-disabled older people in China from 2020 to 2050. Data source: Social Development Research Department, Development Research Center of the State Council.

for at-home nursing (19.80%) and rehabilitation (14.90%) (*34*). A survey on the care needs and satisfaction of older people ages 80 and older indicated that 69.1% of the elderly needed care, 46.7% needed spiritual comfort, 42.3% needed life care, and 31.2% needed home medical care (*35*). In addition, there is a massive need for at-home nursing care among older people who are disabled and have limited mobility. A survey in Chaoyang District, Beijing, revealed that 88% of chronically ill older adults in the community needed home care, but the actual home care available was far from able to meet that need (*36*). After 2030, the ratio of the elderly population in China will approach the current level in developed countries. Even if it reaches the 75th percentile of nurses per 1,000 population in current developed countries, the number of nurses in China will still need to reach about 10,206,500 in 2030, which is a huge gap in nursing resources compared to the number of nurses at the end of 2019 (4.45 million) (*37*). According to a study by Wang *et al.* (*38*), the number of community nurses per 1,000 population in various provinces in China is 0.02-0.45, which is much lower than the current status quo of 2.94 nurses per 1,000 population. In addition, the proportion of community nurses to community health technicians in each province is 31-48%, which differs significantly from the 50% of nurses proposed by the China Health and Welfare Commission (*39*). Furthermore, the number of caregivers in elderly care facilities is also lacking. According to a recent survey conducted in Tianjin, the ratio of elderly to caregivers in elderly care facilities is 1:0.16 (*40*), which is far from the standard of 1:0.8 proposed by the Chinese Health and Welfare Commission (*41*).

3.3. Challenges of the model of care for the elderly

3.3.1. Reduction in traditional family care for older people

In terms of the choice of where to retire, more than 90% of the elderly expect to retire at home. According to the data, 68.4% of older people plan to retire to their own home while or 25.8% plan to retire to their children's home, accounting for 94.16% in total (*42*). In a survey of 6,997 older people, 89.1% chose home-based care and 8.2% chose institutional care, indicating that a vast majority of older people expect to receive home-based care, and home-based care was the most common form of care chosen by these people in China (*43*). Family members are the primary caregivers of older people. The aforementioned survey indicated that older people mainly relied on their children's families to care for them. About 10% of people still take care of their elderly parents. Moreover, 94% of these primary caregivers are family members, including spouses, sons, daughters, and daughters-in-law. Of them, 9.93% still had to care for their elderly parents (*34*).

However, the changing family structure and current economic and social developments have posed serious challenges to this model. Due to the continued decline in the fertility rate, families in China are tending to be smaller, have a core structure, function weakly, exhibit discrete relationships, and involve high risks, leading to issues with care for the elderly. With the continued population trends, the risk of a family having an only child is 4-2-1 and the structure is fragile (*44*). The number of deficient families, including those whose only child has died or been injured, and elderly empty-nest families separated by intergenerational living has increased, greatly challenging the ability of families to withstand pension risks (*45*). Many adult families with only one child lack support and emotional comfort from their offspring; in addition, home care is seriously lacking. A survey indicated (*46*) that 49.03% of children can be with their parents three times a month or even less, while only 29.13% can be with their parents six times a month or more, due to work and other reasons. Therefore, relying solely on the family itself to address the long-term care of older people is almost impossible. The elderly need long-term care due to chronic illness, comorbidities, disabilities, and other health problems, requiring caregivers to have professional medical knowledge and standard nursing skills. Long-term care includes formal and long-term care ranging from diet and daily care to emergency care or rehabilitation (*47*). A survey on long-term care for the elderly in Shanghai in 2010 found that (*48*) 30.3% of families cited a lack of professional nursing knowledge as the biggest difficulty in caring for the elderly with long-term disabilities,

Table 3. Distribution of places for older people in China from 2012 to 2018*

Year	Number of retirement spaces (million)	Growth rate (%)	Number of spaces for the elderly per 1,000 older people (million)	Growth rate (%)
2012	416.5	12.80	21.5	7.50
2013	493.7	18.54	24.4	11.49
2014	577.8	17.03	27.2	11.48
2015	672.7	16.42	30.3	11.40
2016	730.2	8.55	31.6	4.29
2017	744.8	2.00	30.9	-2.22
2018	746.4	2.15	29.9	-3.24

* Data source: *Ref*. (*51*).

precluding family caregivers from maintaining their normal living conditions and also rendering them powerless. Physical and mental fatigue, which imposes a heavy psychological burden on caregivers, is also detrimental to the care of patients (*49*).

3.3.2. Insufficient material and human resources for social services and limited acceptance among the elderly

At present, the home-based model of community care for the elderly is strongly advocated. The infrastructure in some regions is relatively weak due to large regional differences in economics, and the home-based system of community care for the elderly is relatively perfect in developed Beijing, Shanghai, Nanjing, and other places. For inland cities such as Xi'an and Jinan, community home care started late based on the number of places per 1,000 older people. For example, in Hangzhou, Nanjing, Changchun, and Wuhan, the number of places per 1,000 for the elderly has reached more than 30. The number of places for 1,000 older people in Taiyuan is only 5.8. In Lhasa, Harbin, Jinan, and other places, the actual number of older people far exceeds the registered elderly population, and hence there are only about 7 places for every 1,000 older people (*50*). The overall supply of places in elderly care facilities is insufficient, and the occupancy rate is not high. From 2012 to 2018, the number of places for older people in China has increased rapidly while the number of places for older people per 1,000 people initially increased and then decreased (Table 3) (*51*). According to international standards, 50 places are needed per 1,000 older people. Estimates reveal that there are 8 million places for the elderly population in China, but currently, only 2.662 million places are available, representing a gap of 5.4 million places (*52*). The proportion of the elderly population in care facilities is low and declining, dropping from 1.26% in 2012 to 0.72% in 2017. Even older individuals in care facilities in Beijing account for only 1.18% of permanent older residents, and only 16.6% of disabled older people requiring care are in care facilities (*53*). Another survey of 22 pension facilities in China indicated that the highest occupancy rate is 93.57%; the lowest is 58.82%, and the rate is mostly around 60-70% (54).

For older people with poor health, such as incapacitating chronic diseases and comorbidities, two difficulties still exist when they want to obtain institutional care. Most of the current nursing care facilities have separated medical and nursing care, or they offer a low level of medical care, so they fail to meet the basic medical needs of older people; as a result, health care and long-term care of the elderly are severely limited (*55*). Zhao *et al*. (*56*) examined private facilities for the elderly in Qingdao. They found that the current level of medical care was low, and problems with nurses included limited quality, a low salary, and a high turnover rate. Tang *et al*. (*57*) examined all of the social institutions registered with the Civil Affairs Bureau in 13 districts and counties of Nanjing and they analyzed the staffing of facilities for the elderly. Results indicated that facilities for the elderly in Nanjing were relatively poor, with fewer than 30% meeting standards. Most were not staffed with doctors and nurses (64.8% had no doctors, 76.7% had no nurses, 18.5% had no caregiver, and 16.3% of them had no staff). Wang *et al*. (*58*) examined 15 facilities for the elderly in Fuzhou, mainly analyzing the distribution and scale of facilities for the elderly and medical and health care. They found that most facilities for the elderly had a clinic with more than 20 common medicines and simple medical instruments. Combining a literature review and field studies, Chen *et al*. (*59*) selected 17 facilities for the elderly in Hangzhou from which to collect basic information on facilities for the elderly and nursing staff to examine the current state of care for the elderly in facilities. Results indicated that facilities for the elderly in Hangzhou had problems such as a shortage of nursing staff and staff with a low level of education.

In a survey of 6,997 older people, 89.1% chose home care and 8.2% chose institutional care. These figures were similar to the Beijing plan of 90-6-4 care for the elderly (90% of the elderly cared for at home, 6% cared for in the community, and 4% cared for in nursing homes) (*43*). The 90-7-3 plan of care for the elderly proposed by Shanghai (90% of the elderly cared for at home, 7% cared for in the community, and 3% cared for in nursing homes) and the and the 90-

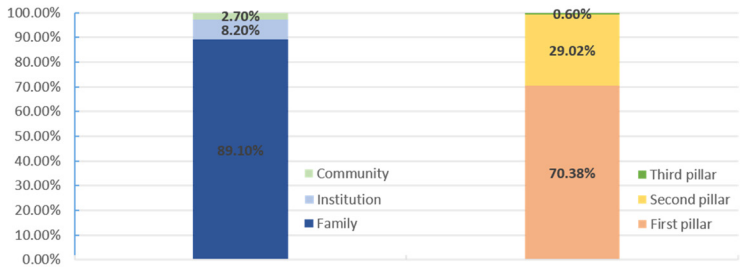

Figure 4.·(A) Comparison of the acceptability of older people in the social pension model. Data source: Analysis of older people's willingness to retire and factors influencing that decision in Shandong Province by Hongjuan Liu [D]; Shandong University, 2019.·**(B) Structure of China's pension funds with three pillars in 2021.** Data source: National Bureau of Statistics public data.

6-4 plan of care for the elderly proposed by Beijing differ (*60*). According to a survey of older individuals in facilities, 77% think they are basically healthy and 40% live in the facility without being cared for. For older individuals who cannot live alone but who do not need full-time care, care in a facility is a huge waste of resources (*61*). In addition, the economy is also an important factor affecting older people's transition to elderly care facilities. A survey of 1,664 older people indicated that 10.52% had no financial resources, 15.87% had no pension, 44.11% had no pension money, and 60.94% had medical needs (*62*).

4. Examination of care for the elderly in the context of aging

The growing number of the elderly population and the lag of care for the elderly has led to increasingly pressing problems related to care for the elderly in China. Hence, the system and model of care for the elderly suitable for national conditions of China need to be urgently explored to rationally allocate pension resources and improve the quality of care for the elderly.

4.1. Development of a multi-tiered pension system

China has developed a three-pillar system of social security for the elderly. The first pillar refers to the national basic pension, the second pillar refers to the supplementary pension from an employer (including an enterprise annuity or occupational annuity), and the third pillar refers to a personal commercial pension (*63*). The first of those three pillars is most prominent (*64*). The gap continues to increase every year as the second and third pillars of the pension system remain limited (Figure 4) and slowly increasing. According to predictions in a relevant report (*65*), China is expected to have a pension deficit of $ 1.27-1.59 trillion over the next 5-10 years, and this will increase further over time. However, the report also points out that the development of the third pillar of the pension system has the weighty task of making up the pension deficit and facilitating the development of the capital market. At present, the third pillar of the pension system is in its early stages of development in China, but it has great potential. In 2018, five ministries and commissions, including the Ministry of Finance, announced the implementation of tax-deferred pension insurance pilot programs in Shanghai, Fujian Province, and Suzhou Industrial Park (*66*). By the end of 2020, the China Banking Regulatory Commission had approved 23 insurance companies to operate tax-deferred pension insurance in 5 batches, with a total of 66 products on the market and a cumulative premium income of $67.62 million; the number of insured totaled 48,800. In the market of social security for the elderly, the balance of social security funds for the elderly reached $ 0.16 trillion yuan at the end of 2019 (*67*). Income from premiums for commercial pension annuity insurance in 2020 totaled $11.30 billion (data from the China State Council Information Office and the Insurance Association of China) and more than $ 92.06 billion in insurance liability reserves had been accumulated; this amount is expected to reach $ 0.95 trillion by 2025 (*68*). Market expansion can be expected in the future. Target retirement funds have steadily increased, growing by $ 10.2 billion as of the end of the first quarter of 2021 (*69*).

4.2. An innovative model of care for the elderly

4.2.1. Integrated elderly and medical care

Integrated elderly and medical care is generally considered to be a health care model that provides life care, health management, and medical care for older people through the integration of medical and elderly care (*70*). The aims are to meet the health care needs of elderly individuals, to improve their health, and to reduce the burden of care for the elderly on family members and society, in addition to improving the allocation of social resources. The 2019 China Health Conference emphasized the promotion of a balanced population and healthy aging, the construction of an elderly care system, the integration of medical care and elderly care systems, and the full-fledged promotion of integrated medical care (*71*).

Li *et al*. (*72*) surveyed Henan Province and found that 55.0% of older individuals needed a combination of medical and elderly care; the greatest need (64.8%) was for follow-up of chronic diseases. The number of people in need of family medical consultations and health care reached 50.6%. Tong *et al*. (*73*) examined a medical facility in Chongqing and found that the model of medical care for the elderly worked well; satisfaction

with the facility among older people was as high as 98%.

In practice, the acceptance of integrated elderly and medical care needs to be further encouraged and promoted in terms of usage and awareness. Wang *et al*. (*74*) surveyed 298 disabled older people in Hangzhou and found that the first 5 services they cited were all related to basic medical care. In addition, more than 50% cited only 4 services, and less than 20% cited 22 services. Results indicated that community support services with a combination of elderly care and medical care were not ideally used by disabled older people in an urban area. A survey of the older people in 12 elderly care facilities in different districts of the City of Xi 'an (*75*) indicated that 68.4% did not know or had never heard of the knowledge and policies related to the combination of elderly care and medical care.

4.2.2. The "Internet+" model of care for the elderly

The Internet+ model of care for the elderly uses Internet technology as a means to integrate artificial intelligence and the Internet with existing home, community, and institutional care for the elderly (*76*). The Internet+ model transforms and upgrades traditional care for the elderly, fully exploring the consumption habits and preferences of the elderly by collecting big data, and the combination of "online and offline" aspects allows vast and varied care and products, facilitating comprehensive care for the elderly. The Internet+ model can involve care for the elderly provided by facilities, communities, and home care centers using "Internet+" technology, or care provided by online personnel using their own network information platforms (*77*). The "Internet+" model of care for the elderly has 4 main elements: an oversight body, a big platform, care providers, and a specialized link The government is the oversight body, civil affairs bureaus create a national platform to provide information on caring for the elderly and enter their basic information, care providers are the companies providing care for the elderly, and a specialized link uses detailed information to improve the accessibility, accuracy, and public approval of care for the elderly (*78*).

"Internet+ medicine" can enhance the innovativeness and continuity of medical care, provide home care to address the problems of older people's limited mobility and bad experiences in hospitals, and also significantly reduce overall medical costs (*79*). Song (*80*) contends that "Internet+" has become one of the most promising "sunrise industries" with the continued development of Internet-based business. In 2010, the National Health Commission of China issued a notice and announced a pilot program to implement "Internet+" medical care (*81*) in six provinces and cities. In recent years, several private providers of "Internet+" care have emerged in China in the form of nursing care platforms covering more than 330 cities. These include the "Internet+" technology platform for older people developed by the Canglang District in Suzhou, China; the comprehensive platform for intelligent care for the elderly in Wuzhen; the Shanghai Vitron Group, a model of home-based care for the elderly incorporating the Internet; Happiness 9; and "Internet+" medical care (*82*). All of these systems are based on increasingly advanced Internet technology and fully focus on the needs of users, namely the elderly, to provide guidance and help with problems and to give the elderly the ability to make more independent choices. "Internet+" reforms and innovation of care for the elderly throughout China and the various new models of care have directly promoted the transformation and upgrading of entities providing care for the elderly and they have highlighted China's new thinking, solutions, and actions to structurally reform the supply side of care for the elderly.

However, the current Internet-based care for the elderly in China is still in its initial stages, and the population in China is rapidly aging. Therefore, the government has proposed a new concept of community-embedded care for the elderly, which encourages the incorporation of the Internet into care for the elderly. However, building of infrastructure construction is lagging somewhat, and personal privacy is at risk due to the use of "big data" (*83*). Moreover, the elderly are less adept at obtaining digital information using mobile terminals, which is also a natural impediment to elderly users in China (*84*). When this platform is being built for the elderly, intelligent terminals and various applications that are suited to the reading habits of and usage by the elderly need to be developed. An infrastructure should be actively built for the elderly, the management of "big data" should be enhanced, intelligent health products should be devised, and online services should be expanded.

4.2.3. Community-embedded care for the elderly

Community-embedded care for the elderly is a form of community care for the elderly. Corresponding functional elderly care facilities are embedded in the community, and corresponding personnel are allocated to provide care to the elderly (*85*). This is a new multi-faceted model of care for the elderly based on the community, integrating the functions and resources of home-based care and institutional care for the elderly (*86*). This model is market-oriented and it operates via competition, actively introducing resources from outside the community and fully examining the resources within the community to provide the elderly with multi-faceted care. This model combines the advantages of traditional family care, community home-based care, and institutional care for the elderly. Scholars have outlined the practical significance of this model, suggesting that this model adapts to requirements at multiple levels and that it varies care for the elderly, it provides solid

support for and a guarantee of family care for the elderly, it integrates community care for the elderly, and it is conducive to standardized and sustainable development (*87*).

In the second half of 2014, Shanghai launched a pilot project of "institutionalized" care for the elderly in the community, with a focus on elderly care homes. By the end of 2017, 127 elderly care homes in Shanghai fully covered the center of the city and the suburbs (*88*). The main approach of the City of Hefei is to embed facilities for the elderly in the community, provide a professional platform for community-based care for the elderly, and further integrate multiple resources such as the family, community, and facilities to create a system of "home + community + medical care + facility" to care for the elderly (*89*). The Chongqing model is to set up a care center in a separate district and to renovate all rented residences, which helps to save construction costs, the Beijing area embeds a community health center inside a care facility and it conclude an agreement with a center to open a "green channel," and Shijiazhuang's model of an "embedded continuing care retirement community" is based on continuing care retirement communities (CCRC) in the US, which are a set of home-based care and support facilities for different age groups and health conditions in a densely distributed community center (*90*).

By incorporating the expertise of facilities for the elderly in community home care, providing professional at-home care and community care for the elderly, and opening up community care centers to provide comprehensive care to the active elderly, community-"embedded" care for the elderly effectively solves the structural problems faced by the traditional model of care, and its unique advantages will allow it become a major trend in the future development of care for the elderly in China.

4.2.4. The elderly care consultant system

The elderly care consultant system is an institutional innovation to refine care for the elderly. Shanghai created the first community elderly care consultant system in May 2018, which was initially promoted in the Xicheng District of Beijing in 2019 to solve the problem of older people who were not informed about policies for the elderly and who had difficulty finding resources (*91,92*). The elderly care consultant system mainly includes two types of basic services and expanded services. Basic services refer to advice on pension policies and resources, while expanded services refers to individual services, including family support and other services. The elderly care consultant system, which has been in effect for more than 2 years, has 4 major roles: to increase awareness of policies related to caring for the elderly, to link to resources from the government, to link to resources from private sources, to link to the community, and to support home care . The elderly care consultant system capitalizes on family involvement in a care for the elderly linked by supply and demand. It can protect the rights and interests of the elderly, coordinate resources in different areas, and create new resources to meet needs (*93*).

Since the introduction of the elderly care consultant system, Shanghai has opened 104 consulting sites and appointed 234 trained pension consultants to serve more than 10,000 people. The on-the-spot response rate remains higher than 94%, which is widely praised by the public and is considered to be a personalized advisor and customized pension service in Shanghai (*94*). The elderly care platform created in Shanghai by the Shanghai Civil Affairs Bureau was officially launched on May 31, 2019 (*95*). The platform covers all sorts of practical information related to care for the elderly, such as official information, the focus of recent policies, a full set of dynamic data, planning reports, instruction guides, and practical projects. The platform aims to use big data and intelligent recommendation technology to enable older people to make independent inquiries in accordance with their own physical condition and financial situation. It provides other information, intelligent guidance with respect to personalized needs, and service suggestions. The aim is to accurately match elderly care facilities and pension services and to customize solutions so that industry can improve the level with which think tanks provide resources and support.

5. Conclusion

In summary, the aging of China's population continues to increase, and there is a multi-faceted need for elderly pensions. Moreover, the need for basic pensions, disease prevention, and health care has also increased. In addition, pension services cannot meet the needs of older individuals due to the lagging development of the insurance system for the elderly in China. The Chinese Government has examined a series of models of care for the elderly to adapt to the development of the aging population and to improve the health status and quality of life of older people. These measures have achieved some results but still need to be examined and improved further.

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Review

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The management of dementia worldwide: A review on policy practices, clinical guidelines, end-of-life care, and challenge along with aging population

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SUMMARY Dementia, with a high incidence rate, fast-developing syndrome and large disease burden, raises challenges to global health and social systems. In this review, in order to elaborate current management and diagnosis statements of dementia, and provide further reference to improve dementia service system, we stated policies, clinical guidelines and management experiences concerning dementia across the world. According to the existing dementia management policies and plans, most countries focus on the following aspects: timely detection of dementia, improvement of service quality, person-centered and integrated dementia services at all stages, dementia awareness and friendliness, and scientific research of dementia. Detection of dementia requires knowledge of medical history and cognitive examination, while dementia diagnosis requires more professional medical examination results. Regarding different types of dementia, multiple international standards are used in practice. The overall goals of dementia treatments include postponing the process of cognitive decline and reducing pain caused by cognitive decline, behavioral and psychological symptoms of dementia (BPSD). Treatments include pharmacotherapy interventions and non-pharmacotherapy interventions. In the end-of-life, palliative care is required to improve the quality of life of people with dementia, and maintain their functions. Challenges exist in reducing the disease burden of dementia in the situation of aging population. There are policy bottlenecks and shortcomings to overcome providing medical care services for people with dementia. We would like to suggest strengthening continuous integrated dementia services, improving community services and management support, encouraging policy and financial support for nursing workers, and better support in the end-of-life.

Keywords dementia, dementia management, clinical practice guideline, international experiences

1. Introduction

The world population suffering from dementia is approximately 50 million, and grows by 10 million per year. The ratio of people with dementia in the elderly population above 65 years old is 5%-8% (*1*). According to World Health Organization (WHO)'s prediction, the global population suffering from dementia will reach 82 million in 2030, and 152 million in 2050. The incidence of dementia increases significantly with aging (Table 1), therefore, incidence of dementia rises along with the increase of average life expectancy. Dementia causes both heavy disease burden and loss of health. In 2019, Alzheimer's disease (AD) and dementia are 25th in the list of disease causes of disability-adjusted life year (DALY), counting 28,352,000 DALYs. In the top 20 disease causes of death, they ranked 7th, causing approximately 1,639,000 deaths, 181% more than the number from the year 2000. Financial burden caused by dementia is also heavy: in 2019, the expenses on dementia worldwide was 1.3 trillion dollars, accounting for 0.76% of worldwide GDP. The direct medical costs were 213.2 billion dollars, 16.2% of total costs; the direct social sector costs were 448.7 billion dollars, 34.2% of total costs; the informal care costs were 651.4 billion dollars, 49.6% of total costs (*1*).

Dementia in the elderly population has a high incidence rate, and a fast developing and heavy disease burden, which brings tremendous pressure on the global health and social systems and needs urgent attention. Currently, treatments for advanced stage dementia are fairly limited. Once the disease develops, it becomes

Table 1. Dementia prevalence and cost in 2019 by WHO region

Regions	Estimated number of people with dementia in 2020 (millions)	Dementia Prevalence in 65+ (%)	Dementia Prevalence in 90+ (%)	Estimated costs of dementia (billion US$)
Worldwide	55.2	6.9	35.9	1,313.4
African Region	1.9	4.4	30.9	15.6
Region of the Americas	10.3	7.9	38.0	364.6
South-East Asia Region	6.5	4.0	21.0	23.9
European Region	14.1	8.5	36.0	438.8
Eastern Mediterranean Region	2.3	5.9	35.0	31.2
Western Pacific Region	20.1	7.6	39.0	439.3

Table 2. Seven-stage model for planning dementia services by WHO

Stages	Dementia services
Pre-diagnosis	• Public awareness, including disease symptoms and where to go for help.
Diagnosis	• Receiving the diagnosis.
Post-diagnostic support	• Information and support for people with dementia and caregivers. • Enable them to make the best use of their current circumstances and plan for the future.
Co-ordination and care management	• Assessing and regularly reassessing the needs of people with dementia. • Arranging care with people with dementia and caregivers.
Community services	• Providing care in homes or community facilities while behavioral and psychological symptoms become more prevalent.
Continuing care	• Continuous care is needed, including hospital care.
End-of-life palliative care	• Special form of continuous care and support when people with dementia are close to the end-of-life.

*The co-ordination and care management stage should apply throughout the whole process of dementia care from diagnosis to palliative care.

progressively worse and cannot be reversed. Therefore, reviewing international experiences will be helpful in understanding the status, diagnosis and treatment of dementia. In this article, we will summarize all aspects of dementia service management, in order to elaborate current status of dementia management and diagnosis, and provide reference to improve the dementia service system.

2. General strategy of dementia

2.1. Dementia services at all stages

Although dementia is currently incurable, disease progression can be delayed and quality of life can be improved through providing targeted medical and nursing care services. From mild symptoms in the early stage to loss of self-care abilities in the advanced stage, people with dementia need the integration of dementia services at family, community, institution and hospital levels, as well as continuous service arrangements covering prevention, treatment, rehabilitation and health care. For the progressive development characteristics of dementia, WHO suggested "Seven-stage model for planning dementia services" (*2*), which divided dementia services into seven stages according to pre-diagnosis, diagnosis and post-diagnosis (Table 2).

2.2. Policy practices of dementia

WHO issued a report "Global action plan on the public health response to dementia 2017-2025" in May, 2017. The first target is to call for 76% of member states (146 countries or territories) to have a strategy tailored to their circumstances by 2025 (*2*). Prior to this, some developed countries have put in place national dementia policies or programs. Some countries have started earlier, such as England (*3*) and France (*4*), which have launched three to four dementia programs. According to statistics, as of May 2021, 34 countries have passed the national level of independent dementia policy or plan, and 31 countries have dementia in existing policy. Most of these policies are included in the overall health and social welfare policy or strategy, 13 countries have separate legislation for dementia, and 42 countries put rights and interests protection of people with dementia into law (*1*).

At present, even in some developed countries, dementia is still a disease that lacks detection, diagnosis, treatment and management. A survey of General Practitioners (GPs) referrals in UK revealed that only 20% of people had cognitive examinations before primary referral to specialist memory services, of which 37% were ultimately diagnosed with dementia (*5*). Therefore, early screening and screening for dementia before diagnosis are crucial. After diagnosis, people with dementia and their families should have access to a continuum of services, both in the community and at the health facility level, which should permeate all aspects of disease management, from diagnosis support to end-of-life care. In order to achieve the ultimate goal of delaying the disease and improving quality of life of people with dementia, some developed countries have introduced

policies to integrate service providers in institutions and services, so that all parties share resources and cooperate to jointly provide people with dementia and their caregivers with distinctive services. As can be seen from established dementia policies or plans, most countries focus on timely detection of dementia, improvement of service quality, people-oriented integration of whole-course services, dementia awareness and community friendliness, and strengthening of dementia research (Table 3, Online Data, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=93*) (*6-29*).

3. Diagnosis and treatment of dementia

3.1. Diagnosis

Detection of dementia requires medical history and cognitive examination to preliminarily determine the existence, severity and nature of cognitive impairment. Commonly used screening tools include MMSE, MoCA (*30,31*), *etc.* Among them, the sensitivity and specificity of MMSE to distinguish elderly with dementia was more than 80% (*32*), which is of high value for screening dementia. MoCA had better sensitivity and specificity than MMSE in identifying MCI and Mild AD (*33*).

More specialized tests are needed to diagnose dementia. There are a variety of clinical classifications of dementia, including by degenerative/nondegenerative disease, by pathological changes, by development of onset and progression, *etc.* Accordingly the classification by degenerative/nondegenerative disease is divided into degenerative and nondegenerative disease dementia. The former mainly includes AD, dementia with Lewy body (DLB), Parkinson disease with dementia (PDD), Frontotemporal lobar degeneration (FTLD), etc; the latter includes vascular dementia (VaD), Normal pressure hydrocephalus (NPH), and dementia caused by other diseases such as craniocerebral injury, infection, immunity, tumor, poisoning and metabolic diseases (*34*). Of these, AD is the most common dementia, accounting for 50-70% of all types of dementia (*35*). The diagnosis of dementia should be based on medical history combined with neuropsychological and other clinical examinations to confirm mental decline. Currently, there are several commonly used international diagnostic guideline for different classifications of dementia (Table 4) (*36-59*).

Take AD for example, choose the diagnostic algorithm from "Chinese Guidelines for the Diagnosis and treatment of Dementia and Cognitive Impairment 2018 (Section 2): Guidelines for diagnosis and treatment of Alzheimer's disease" to elaborate as below (Figure 1).

3.2. Treatment

The overall goal of treatment in dementia is to delay progressive cognitive decline, and reduce the cognitive decline and associated symptoms. Specific treatment includes pharmacotherapy interventions and non-pharmacotherapy interventions. The former, such as the six medications for AD approved by the US Food and Drug Administration (FDA) (*60*), has a certain relief effect on cognition, memory, thinking and other symptoms. The latter includes cognitive training and activities, music or art therapy, physical exercise, diet, *etc.* It is stated in Japanese guidelines that non-pharmacotherapy interventions should take precedence over pharmacotherapy interventions in the treatment of BPSD.

3.2.1. Pharmacotherapy interventions

Currently, although the medications do not cure the disease, they can delay clinical decline, benefit cognitive function, and help reduce symptoms such as memory loss and confusion (*60*). Cognitive, functional, neuropsychiatric, and behavioral symptoms need to be periodically reassessed during medication use to monitor disease progression and make adjustments.

NICE UK guidelines for comparative analysis of clinical efficacy and pharmacoeconomic aspects of common medications for the treatment of AD – "Donepezil, Galantamine, Rivastigmine and Memantine for the Treatment of Alzheimer's Disease" was first published in 2011 and updated several times in 2014, 2016 and 2018 (*61*), respectively. In 2011, the Chinese Guidelines for the Diagnosis and Treatment of Dementia and Cognitive Impairment (Section 5): Treatment of Dementia (*62*) was released, and a comprehensive update was made in 2018 (*44*), recommended the diagnosis and treatment of AD. The clinical pharmacotherapy guidelines of the UK, US, China and Japan are summarized below (Table 5) (*37,44,60-62*). Cholinesterase inhibitors (ChEIs) are generally recommended for mild to moderate dementia, while Memantine is recommended for severe dementia. The combination of Memantine and Donepezil is recommended for severe AD in three countries except for the UK.

3.2.2. Non-pharmacologic interventions

Non-pharmacologic interventions include cognitive training and activities such as reading, playing chess or canasta, music or art therapy, reminiscence therapy, physical exercise including aerobic exercise (such as walking, swimming) and anaerobic exercise (such as weightlifting), *etc.* These interventions may have a positive impact on cognition and physical function. It is recommended to have more brain-healthy foods (such as nuts, berries, green leafy vegetables, fish) or a Mediterranean diet. However, people with moderate to severe dementia may have difficulty engaging in cognitive functions, they should be limited in physical

Table 4. Diagnostic guidelines of dementia (by degenerative/nondegenerative disease)

Classification	Year	Area	Diagnostic guidelines	Drafted by	Content*
Degenerative dementing disorders					
AD	1984	America	NINCDS-ADRDA (*36*)	National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association, NINCDS-ADRDA	D&T
	2002, 2010, 2017	Asia	Clinical Practice Guideline for Dementia (*37*)	The Japanese Society of Neurology Guideline Executive Committee	D&T+E+P+Pa+F
	2007, 2014	Europe	IWG-1 (*38*), IWG-2 (*39*)	International Working Groups, IWG	D&T+Pa
	2010	Asia	Clinical practice guideline for dementia (*40*)	The Clinical Research Center for Dementia of South Korea (CREDOS)	D&T
	2011, 2018	America	NIA-AA 2011 (*41,42*), NIA-AA 2018 (*43*)	National Institute on Aging-Alzheimer's Association, NIA-AA	D&T+Pa
	2018	Asia	Chinese Guidelines for the Diagnosis and treatment of Dementia and Cognitive Impairment (*44*)	Writing group for the Diagnosis and treatment of Dementia and Cognitive Impairment in China, Cognitive Disorders Professional Committee of Neurology Branch of Chinese Medical Doctor Association	D&T+E+P+Pa
FTLD					
bvFTD	2011	Global consensus	Revised diagnostic criteria for the behavioural variant of fronto-temporal dementia (*45*)	Rascovsky K, *et al.* the international Behavioral Variant FTD Criteria Consortium, FTDC	D&T
PNFA	2011	Global consensus	Classification of primary progressive aphasia and its variants (*46*)	M L Corno-Tempini *et al.*	D&T
DLB	1996, 1999, 2005, 2017	Global consensus	DLB Consortium 2005 revised criteria (*47,48*) Diagnosis and management of dementia with Lewy bodies Fourth consensus report of the DLB Consortium (*49*)	The DLB Consortium	D&T+Pa
PDD	2007	Global consensus	Clinical diagnostic criteria for dementia associated with Parkinson's disease (*50*)	Murat Emre, *et al.*	D&T+E+Pa
Nondegenerative dementing disorders					
VaD	1992	America	Diagnostic criteria for ischemic vascular dementia by Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) (*51*)	Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) in California	D&T
	1993	Global consensus	International Statistical Classification of Diseases and Related Health Problems (ICD-10) (*52*)	WHO	D&T
	1993	America+Europe	NINDS-AIREN diagnostic criteria (*53*)	National Institute of Neurological Disorders and Stroke (NINDS), Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN)	D&T
	1994, 2013	American	Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-4) (*54*), 5th Edition (DSM-5) (*55*)	American Psychiatric Association	D&T
	2011	America	ASA/AHA 2011 criteria (*56*)	American Stroke Association, American Heart Association	D&T+E+P+Pa
	2011, 2019	Asia	Guidelines for the diagnosis and treatment of vascular cognitive impairment (*57,58*)	Writing group of Dementia and Cognitive Impairment, Chinese Society of Neurology	D&T+E+P+Pa
	2014	Global consensus	Diagnostic criteria for vascular cognitive disorders (Vas-Cog criteria) (*59*)	International Society for Vascular Behavioral and Cognitive Disorders (VASCOG)	D&T

*D&T, diagnosis and treatment; E, epidemiology; P, prevention; PA, pathogenesis; F, follow-up.

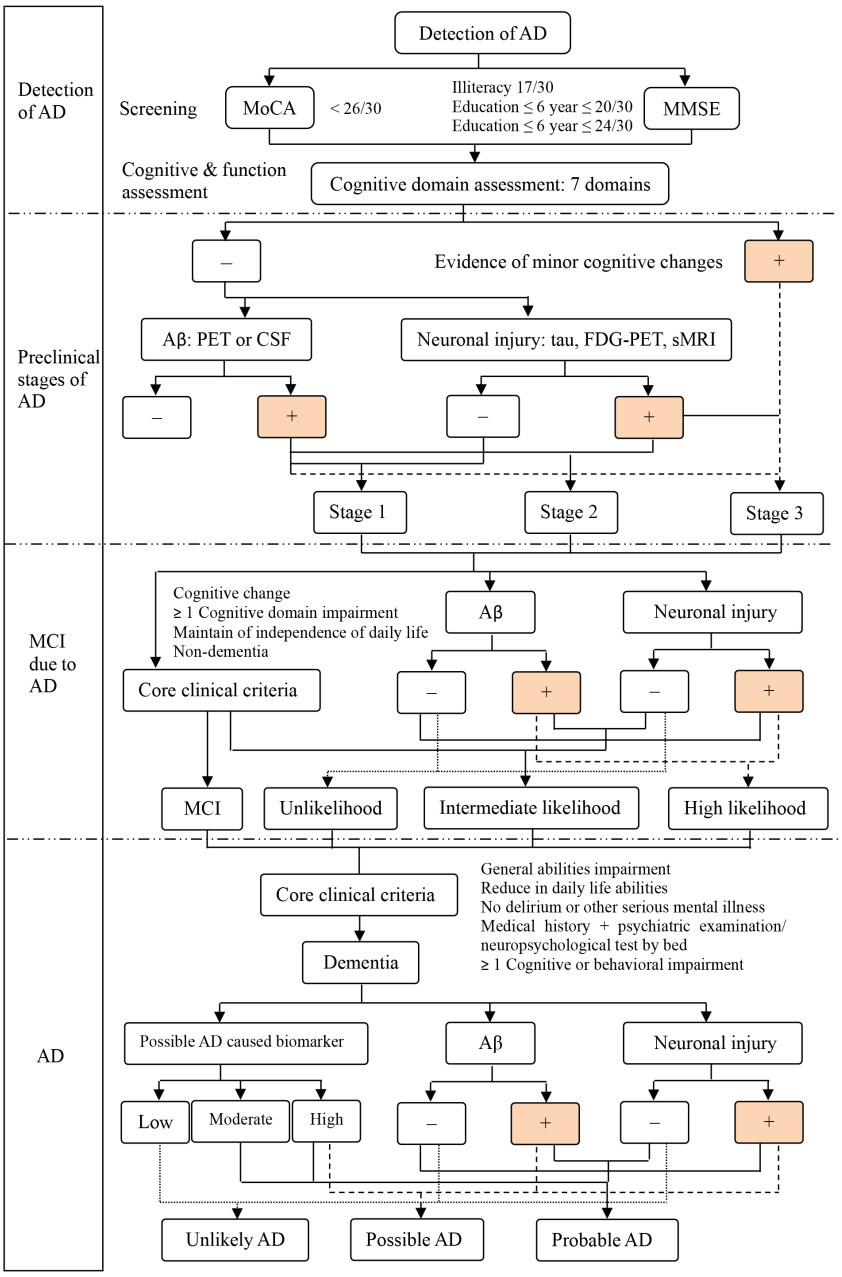

Figure 1. The diagnostic algorithm for AD in Chinese Guidelines for the Diagnosis and treatment of Dementia and Cognitive Impairment 2018. AD, Alzheimer's disease. –: Negative/none/indeterminacy; +: Positive.

and social activities when they can no longer safely and effectively participate.

4. Continuous care in the end-of-life

When people with dementia approach the end of their lives, continuing care is needed because the symptoms of disease are getting worse. The care includes continuing care, that is, providing care to people who can no longer stay at home (such as different forms of support or institutional care), and palliative care to people at the terminal stage of disease (*63*). The European Association for Palliative Care White Paper on the suitability of palliative care for people with dementia states: "Improving quality of life, maintaining function and maximizing comfort are not only the objectives of palliative care, but also applicable to dementia disease progression" (*64*). Attempts have been made in some countries, such as Japan, which revised its National Dementia Plan in January 2015 to support end-of-life care by strengthening social and health collaboration (*65*); Finland also proposed in the "National Memory Programme 2012-2020" to comprehensively evaluate the health and function of people with dementia and provide them with quality palliative care when prolonging life is no longer meaningful (*66*).

The Palliative Care for Older People (PACE) project is a European Union (EU)-funded project that runs

Table 5. Comparison of medications for AD in 4 countries in 2018

Country	Medications	Cost-effectiveness analysis	Polypharmacy
UK (NICE) (*61*)	• Mind to moderate: ChEIs ○ Donepezil, rivastigmine, Galantamine • Severe: NMDA receptor antagonist ○ Memantine	In combination with clinical efficacy and economy, it is recommended that the medication with the lowest price be the best choice among ChEIs	The combination of Memantine + ChEIs is not recommended
US (FDA) (*60*)	• Delay clinical decline: Aducanumab • Treatment of symptoms: √ Cognitive symptoms (memory and thinking) ○ All stages of AD: Donepezil ○ Mind to moderate: Rivastigmine, Galantamine ○ Moderate to severe: Memantine, Memantine + donepezil √ Non-cognitive symptoms (behavioral and psychological): Suvorexant	–	A combination of Memantine + ChEIs – Donepezil may be an option for moderate to severe AD
China (guideline) (*44, 62*)	• Mind to moderate: ChEIs ○ Donepezil, Rivastigmine, Galantamine and Huperzine A • Severe: Memantine • Ancillary drugs: traditional Chinese medicine (Ginkgo biloba extract), Cerebroprotein Hydrolysate	– Mainly based on the clinical efficacy of the medication	• Moderate to severe AD can choose to use Memantine, or Memantine + Donepezil, rivastigmine as combination • The combination of ChEIs + Memantine is especially recommended for severe AD with significant psychobehavioral symptoms
Japan (guideline) (*37*)	• Mind to moderate: ChEIs ○ Donepezil, Galantamine, Rivastigmine • Moderate to severe: NMDA receptor antagonist ○ Memantine, ChEIs + Memantine, Donepezil 5-10 mg	–	ChEIs – Donepezil + Memantine combination for severe AD

*Japan guidelines is in 2017.

from 2014 to 2019. Palliative care in nursing homes and facilities in EU countries was compared from three levels: the macro, medium and micro level (*67*). Macro level includes policy, documents, strategies, guidelines, and legislation. For example, the UK's National End-of-life Care Strategy that was introduced in 2018, specifically proposed the provision of palliative care in nursing homes as places for elderly people to live at the end-of-life; "Patients' Rights and the End-of Life Act" published in France in 2005, clearly states the objectives of palliative care in nursing homes. The medium level includes: *i*) Education and training. For example, Denmark and Germany have improved ability of palliative care in nursing home staff through multidisciplinary training programmes; *ii*) Service pathway, service list and service model. For example, Iceland has introduced the Liverpool Care Pathway into institutions in downtown Reykjavik, and Sweden has adopted palliative registration to ensure the regularity and quality of service utilization; *iii*) Service development studies, such as the Federation Palliative Care Flanders guidelines introduced palliative care in nursing homes; Micro level focuses on the proportion of nursing homes providing palliative care. Austria, Belgium, Ireland, Netherlands, Sweden, Switzerland, and UK have a relatively high proportion of nursing homes directly providing palliative care among the EU countries. The study found that the delay of implementation of palliative care was a common phenomenon in the surveyed EU countries (*68*). Even in countries with a more developed palliative care system, the quality of death and quality of life at the end-of-life in nursing homes were not optimistic (*69*).

5. How to address the challenge of dementia disease burden in the context of aging population

At present, many countries are turning into an aging society in which dementia, a disabled and semi-disabled aging population continually increases. Dementia, as a disease with high prevalence and heavy burden in the elderly population, will face severe challenges in the future. Although the government and people of some countries have made active responses, there are still policy bottlenecks and shortcomings to be overcome in the medical care services for people with dementia due to the relatively high requirements for continuity of services for the disease.

5.1. Continuous, holistic and integrated care

As proposed by Alzheimer's Disease International (ADI), care for people living with dementia need to be "continuous, holistic and integrated" (*70*). Continuous care means that the treatment, care plans and needs support must be continuous throughout the disease

progress; holistic care means treating the whole person instead of single conditions, organ or system, with close attention to unique preferences and values; integrated care means the integration of health and social services across different levels of care provided by different providers (*70*). WHO defines "integrated care" as "the concept of integrating related organizations providing input, service, and management, as well as diagnosis, treatment, care, rehabilitation and health promotion as a whole. Integration is a means to improve service accessibility, quality of service, patient satisfaction and efficiency" (*71*). Based on international experience, integration includes horizontal and vertical integration. Horizontal integration is the integration of different systems within the same level of services, such as health and social services. Vertical integration is the integration among different levels of services, or different professional levels, such as primary, secondary and tertiary health services. Due to the progressive development of dementia, providing continuous, holistic and integrated services will help people with dementia maintain a higher quality of life.

5.2. Community services and administrative support

Currently, long-term care policy for the elderly in many countries and regions advocate the concept of "Aging in Place", which means living at home in the community and getting all kinds of services needed from home (*72,73*). As a vulnerable group, the elderly with dementia have special service needs. Living in their familiar environment makes the elderly feel relaxed, which is conducive to their maintenance of functions, and saves social resources at the same time. In this case, we should focus on grass-roots units and strengthen community services and management. For a high-risk elderly population, we must carry out early screening services and take intervention measures; For people in the middle stage of disease and end-of-life, it is suggested to establish a cross-professional service team to provide physical and life care, and maximize the protection of the physical health and self-care ability of the elderly.

5.3. Caregiver support and financial incentives

Studies show that many caregivers of people with dementia are family members. For instance, in China, care for the elderly with dementia is mainly provided by family members, especially spouses (*74,75*), and their daily caring time lasts up to 11 hours (*76*). Most of the spouses are older people as well, and such a long period of intensive caring is a great burden on their physical and mental health. From international experience, many countries have set up support programs for caregivers, including help hotlines and respite services. First, it is suggested that the priority is to improve caregivers' awareness and knowledge, and provide support. To hold courses, promoting caring methods for dementia, caregivers' self-adjustments and finding appropriate social resources. Second, to set up dementia hotlines and establish mutual assistance organizations to support caregivers. Third, to adopt appropriate economic incentives. For informal caregivers, special funds can make up for their extra time; for formal caregivers, the treatment level can be improved. Fourth, to explore the establishment of respite services.

5.4. Strengthen support for people in end-of-life

WHO indicates, in the terminal stage of dementia, the lack of service comes from two aspects: too much intervention with little effect (tube feeding and laboratory tests, use of restriction measures and intravenous medications), and too little intervention (poor pain control, dehydration and malnutrition, emotional and social neglect) (*77*). There is an urgent need to improve end-of-life care for people with dementia, including interventions for restlessness, constipation and pain, which can improve quality of life, as well as reduce unnecessary tests and costs (*77*). The support for people with dementia in end-of-life includes not only strengthening the content of palliative care (*78*), but also the support for the families (*79*) and education for medical and caregiving personnel (*80*).

6. Conclusion

In this article, we reviewed the policies, clinical guidelines, and management experiences related to dementia services at all stages, including policy practices of dementia from 10 countries, and 10 diagnostic guidelines of dementia published globally from 1984 to 2019. At present, there are many commonly used diagnostic criteria for different types of dementia worldwide, since AD is the most common type of dementia, this article summarized the diagnostic algorithm for AD in Chinese Guidelines for the Diagnosis and treatment of Dementia and Cognitive Impairment 2018, and compared the medications for AD to that in 4 countries, to provide clinicians with up-to-date information.

At present, there are two main problems in the management of dementia: one is in the operational level. Early screening is important because dementia symptoms generally progress in stages and are not curable. However, there are still major deficiencies in the early screening of dementia worldwide, resulting in many people with underlying dementia who are still in need of timely intervention. Second, most people lack scientific understanding and awareness of dementia, and society is not friendly enough for people with dementia to live in. There have been explorations of dementia-friendly communities worldwide, but most of them are scattered in various regions, and the consensus of the whole

society has yet to be formed; the other is at the scientific research level. Current pharmacotherapy interventions for dementia are extremely scarce, and further scientific research is needed.

Dementia is a disease with a high incidence of dementia among the elderly population, a rapid development trend, and a heavy disease with economic burden. It ranks 7th among the top 20 causes of death in the world. Summarizing and comparing policies and clinical guidelines related to dementia services at all stages may help to improve the management of dementia with precision. However, further research is needed to improve dementia management outcomes and help guide physicians to make better decisions in the detection, diagnosis, treatment, and continuous care of dementia in the future.

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Review

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Conversion therapy with an immune checkpoint inhibitor and an antiangiogenic drug for advanced hepatocellular carcinoma: A review

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SUMMARY Hepatocellular carcinoma (HCC) has been the fifth most common malignancy worldwide and is the second most common cause of tumor-related mortality globally. In China, a high proportion of patients with HCC present with an advanced stage of the disease, so HCC is a major challenge to the healthcare system and a substantial socioeconomic burden. The last decade has witnessed an expansion of the treatment landscape for HCC. Various approaches have been explored as potential conversion therapies for advanced HCC. Despite controversies, mounting data have indicated that successful conversion therapy followed by subsequent surgery is achievable in a population of patients with advanced HCC. This conversion therapy is a safe and promising treatment strategy to prolong long-term outcomes. Based on preliminary research, this review has assembled and summarized current clinical experience with and evidence of the efficacy of conversion therapies followed by subsequent surgery for advanced HCC.

Keywords hepatocellular carcinoma, conversion therapy, immune checkpoint inhibitors, antiangiogenic drugs, subsequent surgery

1. Introduction

Hepatocellular carcinoma (HCC) has been the fifth most common malignancy worldwide, with over 500,000 new cases every year, and it represents the second leading cause of tumor-related mortality globally (*1-12*). There is a considerable geographical imbalance in the incidence of HCC. The incidence of HCC has decreased in certain countries or areas where it was high (East Asia and sub-Saharan Africa) but it has increased in some countries or areas where it was low (India, the Americas, Oceania, and southern European countries) (*8*). Data from 2018 have indicated that the estimated global incidence of primary liver cancer (as the principal type of primary liver cancer, HCC represents more than 80% of the total) per 100,000 person-years was 9.3% and its mortality rate was 8.5% (*1,2,7-9*). Due to the prevalence of infection with the hepatitis-B virus, HCC is particularly endemic in China (*13*). Data on Chinese patients with HCC from 2003 to 2015 have indicated that there is substantial room for improvement in long-term outcomes, with a five-year overall survival rate of merely 12.5% (*14*). Liver resection remains the first-line treatment for early-stage HCC, with a five-year overall survival rate of around 40 to 50% (*4,15*). However, around 44-62.2% of the population with HCC in China has cancer of an advanced stage according to the Barcelona Clinic Liver Cancer (BCLC) classification at initial diagnosis. (*14,16*) For patients with such advanced HCC, palliative locoregional or systemic treatments, or even palliative supportive care, are recommended over surgical resection in most HCC guidelines (*4,17*). Outcomes are unsatisfactory, with a median overall survival of around 8-12 months. Even for certain groups of patients with advanced HCC who underwent initial surgical resection, the postoperative prognosis is quite poor. Hence, HCC poses a major challenge to the healthcare system and a substantial socioeconomic burden in China (*16,18*).

The last decade has witnessed profound progress in therapeutic paradigms for advanced HCC (*5,13,16*). A combination of an immune checkpoint inhibitor (ICI) and an anti-angiogenic drug (AAD) has promising use in

cancer treatment. A combination of an ICI and an AAD has yielded inspiring results in the treatment of advanced HCC compared to previous approaches, setting a new benchmark with an objective response rate (ORR) of 33.2-46.0% and a disease control rate (DCR) of 72.3-88% and a complete response (CR) rate of 8.6-11% and median overall survival of 17 months for unresectable HCC (*14,16*). Moreover, the combination of an ICI and an AAD can be utilized as a conversion therapy for advanced HCC, which would change unresectable advanced HCC into resectable tumors and offer patients the possibility to undergo subsequent radical surgery (Figure 1) (*16,19*). As early as 2016, the current authors initiated conversion therapy for unresectable HCC using an ICI and an AAD, and inspiring outcomes were obtained. Based on Chinese practices and discussions among domestic experts, a consensus among Chinese experts has also been reached (*16*). The current review has mainly assembled and summarized current clinical experience with and evidence of the efficacy of conversion therapy (with an ICI and an AAD) followed by subsequent surgery for advanced HCC. This review also discusses several issues with conversion therapy and subsequent surgery for advanced HCC.

2. Necessity of conversion therapy for advanced HCC

Currently, there is little controversy about the definition of advanced HCC in domestic and foreign guidelines. Macrovascular invasion and extrahepatic metastasis are vital elements in the definition of advanced HCC. Table 1 summarizes the relevant information on advanced HCC in three domestic or international guidelines (*8,9,20*). Advanced HCC accounts for 44-62.2% of all patients with HCC at initial diagnosis. The survival rate of such patients is quite low, greatly limiting improvement of the prognosis for HCC. Therefore, there is a pressing need for conversion therapy for advanced HCC. In recent decades, the treatment landscape for advanced HCC has expanded. Local or systemic treatments include transarterial embolization (TAE), transarterial chemoembolization (TACE), transarterial radioembolization (TARE), hepatic arterial infusion chemotherapy (HAIC), stereotactic body radiation therapy (SBRT), localized concurrent chemoradiotherapy (CCRT), ablation, tyrosine kinase inhibitors (TKIs), ICIs, and their combined use. Despite these various approaches, the prognosis for advanced HCC has barely changed (*16*). Data have indicated that the DCR of TAE and TACE mostly ranges from 3.9 to 37.9%, with a median overall survival of 5-15.5 months (*21,22*). Special care should be given to patients with portal vein tumor thrombosis. For such patients with a blocked portal vein, TACE may further aggravate liver ischemia and lead to liver failure (*23*). TARE with yttrium-90 microspheres is a liver-directed therapy for hepatic tumors. Indications for TARE are mainly downsizing tumors, increasing future liver remnant, and bridging to transplantation. For advanced HCC, TARE is used for palliation or delayed progression of disease (*24*). The role of TARE in advanced HCC has been the subject of two randomized trials comparing sorafenib and TARE. No significant difference in median overall survival was evident (8.8 months in the TARE group versus 10

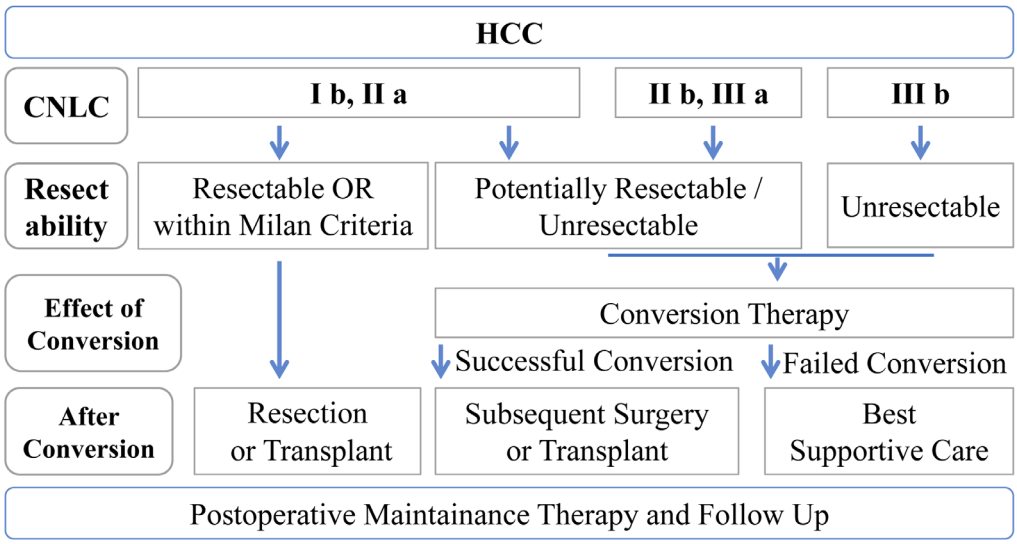

Figure 1. Algorithm for Conversion Therapy for Hepatocellular Carcinoma. CNLC: China Liver Cancer stage; Milan criteria: diameter of a single tumor ≤ 5 cm, the number of tumors ≤ 3, all ≤ 3 cm in diameter, and without angioinvasion or extrahepatic involvement; Resectable: R0 resection, sufficient future liver remnant at initial diagnosis; Potentially Resectable: preoperative predicted functional residual liver volume and liver function reserve at borderline level or with doubtful postoperative oncological benefit; this corresponds to patients with mild to moderate impairment of liver function reserve in the following stages: certain groups of patients with Barcelona Clinic Liver Cancer -B, C, or CNLC-IIIa with intrahepatic portal vein and/or hepatic vein tumor thrombus, or patients with CNLC-IIIb with resectable extrahepatic lesions; Unresectable: one of three situations: insufficient future liver remnant after surgery, tumor thrombus in main portal vein or hepatic vein, or unresectable extrahepatic lesions are present.

Table 1. Definition and recommended treatment for advanced HCC in guidelines

Guideline	Definition/staging	Treatment	Survival
AASLD guidelines	Macrovascular invasion and/or metastatic disease	Local or Systemic therapy*	–
EASL guidelines	Macrovascular invasion (either segmental or portal invasion) or extrahepatic spread (lymph node involvement or metastases) BCLC stage C	Local or Systemic therapy*	Median survival of 6-8 months; 1-year OS 25%
Chinese guidelines	Macrovascular invasion and/or metastatic disease CNLC stage IIIa or IIIb	Local or Systemic therapy*	1-year OS 12-38.3%

HCC: Hepatocellular carcinoma; AASLD guidelines: the American Association for the Study of Liver Diseases Guidelines for the Treatment of Hepatocellular Carcinoma 2018; EASL Guidelines: the European Association for the Study of the Liver Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018; Chinese Guidelines; Chinese Guidelines: Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2022 Edition); OS: Overall survival; BCLC stage: Barcelona Clinic Liver Cancer stage; CNLC stage: China liver cancer stage; *depending on the extent of vascular invasion and/or metastatic disease, the severity of underlying cirrhosis, and the performance status of the patient.

Table 2. Differences between conversion therapy and neoadjuvant therapy for HCC

Items	Subject	Aim	Methods	Observation time	End point
Conversion therapy	Unresectable tumor; #Outside liver transplantation criteria	To make surgery or a transplant feasible and improve overall survival	Local or Systemic therapy (Modalities often overlap)	3-6 months (median of 5 cycles with an ICI + an AAD)	ORR, TTP, OS, RFS Rate of subsequent surgery
Neoadjuvant therapy	Resectable tumor	To simplify surgery and improve long-term results To decrease tumor progression (and dropout) from transplantation waiting list		1.5-3 months (no longer than 4 months)	OS, RFS

HCC: hepatocellular carcinoma; ICI: immune checkpoint inhibitors; AAD: anti-angiogenic drugs; ORR: objective response rate; TTP: time to progression; OS: overall survival; RFS: recurrence-free survival; #mainly referring to the Milan Criteria, diameter of a single tumor ≤ 5 cm, the number of tumors ≤ 3, all ≤ 3 cm in diameter, and without angioinvasion or extrahepatic involvement.

months in the sorafenib group) (*24*). Developments in radiation oncology have facilitated the advancement of SBRT. Studies have suggested that SBRT yielded a high local control rate (2-3 years: 70-100%) and a high overall survival rate (60-70%) in early-stage HCC (*25,26*). Generally, SBRT was regarded as an alternative to other approaches, such as hepatectomy, TACE, and ablation (*8,27*). Controversy still exists about hepatectomy for advanced HCC. The reported median recurrence-free survival after surgery was only 1.5 to 10.0 months, the one-year recurrence rate was 34.0-86.7%, the three-year recurrence rate was high as 85.0-95.4%, and the overall recurrence rate as high as 85.0-97.2%. Median overall survival is 4.8-19.5 months, and the one-year, three-year, and five-year survival rates are 28.6-50.0%, 12.5-22.7%, and 4.0-23.8%, respectively (*16,21,28,29*) . Early recurrence seriously affects the prognosis for advanced HCC. Studies have confirmed that cancer in a late stage is an independent risk factor for a poor prognosis after HCC hepatectomy.

The fundamental reason for a poor prognosis for advanced HCC lies in the limited oncological benefits from the aforementioned local, systemic or surgical treatments. Due to the harmful biological behavior of advanced HCC, none of these treatments can reduce the high recurrence rate and result in a radical cure. Therefore, the current authors propose to focus on the survival benefits for patients and to explore conversion therapy with a combination of an ICI and an AAD for advanced HCC. Conversion therapy for advanced HCC mainly includes the following two connotations: a) conversion to surgical resectability and b) the possibility of an oncological benefit (*16,30,31*).

3. Current status of conversion therapy for advanced HCC

In the treatment of HCC, conversion therapy should be distinguished from neoadjuvant therapy. Both of the two concepts are vital steps in preoperative therapy for intermediate or advanced HCC (*16,18,32-35*). Although there are still debates over the confusing overlap of the two concepts, the differences between conversion therapy and neoadjuvant therapy for HCC are briefly summarized in Table 2.

Unlike neoadjuvant therapy, conversion therapy in

Table 3. Brief summary of conversion approaches for advanced HCC

Treatment	ORR	Conversion rate	Rate of subsequent surgery	Rate of grade 3-4 adverse events	Outcome
ALPPS	–	–	91%	11.1%*	1-year RFS 47.6% 1-year OS 64.2%
TAE, TACE	3.9-37.9%	–	9.8-12%	30%	1-year RFS 36-68%
TARE	–	20.8%	9%#	17.1%	5-year OS 86%
HAIC	28.6%	–	11.7%	19%	–
SBRT	–	–	5.7%	0.6%	1-year OS 36.2-56%
HAIC + CCRT	–	–	16.9%	–	1-year RFS 57.7%
TKI + Local Therapy	5.7-45.0%	–	14.3%	–	1-year OS 46.5-61%
Atezolizumab+ Bevacizumab	29.8%	–	–	56.5%	1-year OS 67.2%
Concurrent chemo/ radiotherapy	–	6.8%	–	–	5-year OS 49.6%
ICI+ TKI		51%	30.6%	6.1%	1-year RFS 61% 1-year OS 74%

HCC: hepatocellular carcinoma; ORR: objective response rate; ALPPS: associated liver partition and portal vein ligation for staged hepatectomy; TAE: transarterial embolization; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; HAIC: hepatic arterial infusion chemotherapy; SBRT: stereotactic body radiation therapy; CRRT: concurrent chemoradiotherapy; TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor; RFS: recurrence-free survival; OS: overall survival. #Includes the rate of subsequent liver transplantation and liver resection; *90-day mortality rate; Adverse events are grouped in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Table 4. Targets of tyrosine kinase inhibitors

Tyrosine kinase inhibitors	Bevacizumab	Ramucirumab	Sorafenib	Lenvatinib	Regorafenib	Cabozantinib	Donafenib
Target	VEGFA	VEGFR2	VEGFR1–3 PDGFR RAF KIT	VEGFR1–3 PDGFR FGFR1–4 RET	VEGFR1–3 PDGFR RAF FGFR1–2	VEGFR1–3 MET RET	VEGF PDGF RAF MEK ERK

VEGFA: vascular endothelial growth factor A; VEGFR: vascular endothelial growth factor receptor; PDGFR: platelet-derived growth factors; FGFR: fibroblast growth factor receptor.

advanced HCC is not an emerging treatment approach or a new concept (*36-40*). A previous study suggested that 139 of 1,085 patients with unresectable HCC enrolled from 1958 to 2003 were converted and underwent subsequent surgical resection, resulting in a five-year survival rate of 48.7% (*41*). Now, with multiple systemic agents in development, various approaches have been explored as potential conversion therapies for advanced HCC. Specific methods include associating liver partition and portal vein ligation for staged hepatectomy, ablation, TACE, HAIC, SBRT, CCRT, TARE, TKIs, ICIs, and multimodality treatment approaches (*16,18,42,43*). Conversion outcomes of various approaches are cited in Table 3 (*16,18,42,44-46*). Despite controversies, mounting data have indicated that successful conversion treatment followed by subsequent surgery is achievable in the population of patients with advanced HCC (*47*).

4. A combination of an ICI and an AAD offers hope as a conversion therapy for advanced HCC

In recent years, ICIs and AADs have y encouraging outcomes in the treatment of various solid tumors. New drugs including multikinase inhibitors (such as lenvatinib; target of TKIs are summarized in Table 4) and programmed cell death protein 1 (PD-1 as well as programmed cell death ligand 1 and its inhibitors such as pembrolizumab and atezolizumab; combinations of an ICI and an AAD are summarized in Table 5 (*11,48-50*)) have proven effective in the treatment of advanced HCC and have been successively recommended by domestic and international HCC guidelines (*16,46,51,52*). The ORR of an ICI or AAD alone is only 9.2-24.1% (49, 53). Recent studies have confirmed that the combined use of an ICI and an AAD could further improve ORR in advanced HCC, achieving an efficacy of "1+1 > 2" (*16*). For unresectable HCC, a combined regimen was reported to have a DCR rate of 33.2-46.0% (*25*). A combination

Table 5. Combinations of immune checkpoint inhibitors and anti-angiogenic drugs

ICI	Combination	Number of patients	ORR	Survival (month)	Recommended as
anti PD-1	Lenvatinib + Nivolumab	30	54.2	73.9 (PFS)	First line
anti PD-1	Lenvatinib + Pembrolizumab	100	36.0	8.6 (PFS)	First line
				22 (OS)	
anti PD-1	Apatinib + Camrelizumab	70	34.0	5.7 (PFS)	First line
				20.3 (OS)	First line
anti PD-1	Regorafenib + Pembrolizumab	35	29	6.8 (PFS)	First line
anti PD-1	Anlotinib + Penpulimab	31	24	5.4 (PFS)	First line
				21.5 (OS)	/Second line
anti PD-1	Cabozantinib + Nivolumab	36	19	1-year OS 12-38.3%	First line
anti PD-1	*Bevacizumab + Sintilimab	380	21	4.6 (PFS)	First line
anti PD-L1	*Bevacizumab + Atezolizumab	336	30	19.2 (OS)	Second line
anti PD-L1	*Tremelimumab + Durvalumab	74	24	18.7 (OS)	

ICI: immune checkpoint inhibitors; ORR: objective response rate; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; PFS: progression free survival; OS: overall survival. *not a combination of immune checkpoint inhibitors and anti-angiogenic drugs.

of an ICI and an AAD could involve a synergistic mechanism that can not only improve the immune microenvironment but also promote the normalization of immune cell function (*5,13,54*). The degree of tumor infiltration by immune cells can determine the efficacy of immunotherapy. A recent study has indicated that tumors can be categorized into a 'high T cell' group (also called hot tumors) or a 'low T cell group (also called cold tumors) (*55*). Combination therapy (in addition to local therapies) could facilitate immune cell infiltration into 'low T cell' tumors, thus converting 'cold' tumors to 'hot' ones and enhancing the treatment response (*56*). This synergistic mechanism may involve multiple mechanisms, including improved vascular normalization for drug delivery and immune cell infiltration, activation of various antitumor immune cell subsets, and/or inhibition of immune cell types with pro-tumor activity. One example is the vascular endothelial growth factor (VEGF) pathway; inhibition of VEGF signaling also combined with the action of an ICI to enhance the antitumor immune cell response and inhibit key immunosuppressive pathways (*56-58*). This enhanced anti-tumor action has been observed in mouse tumor models using multikinase inhibition with lenvatinib plus anti-PD-1 inhibition. In immunocompetent mice, treatment with a multikinase inhibitor and anti-PD-1 antibodies yielded more significant tumor regression and a greater ORR in comparison to either approach alone (*59,60*). Research results indicated that a multikinase inhibitor could reduce the tumor PD-L1 grades and Treg differentiation to promote anti-PD-1 function (*61,62*). Moreover, a phase Ib study of lenvatinib plus pembrolizumab implied that multikinase inhibition with anti-PD-1 inhibition resulted in a confirmed response rate of 46% according to mRECIST, which gives credence to the improved antitumor activity and increased tumor sensitivity of combined use (*48*). Hence, synergistic action is conducive to improved efficacy.

Moreover, unlike traditional invasive treatments such as HAIC, TACE, and SBRT that require hospitalization, the combination of an ICI and an AAD is simple and convenient. The treatment can be completed in a day ward or at home. The incidence of serious adverse events is relatively low and recovery can be achieved through drug withdrawal or hormone therapy. Research by the current authors has indicated that a combination of an ICI and an TKI resulted in an adverse event incidence of about 46.9%, most of which are below grade three (*63*).The incidence of grade three or four adverse events was 6.1% which is significantly lower than that of other treatment modalities (*18,42,44-46,64-66*). Adverse events are grouped in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (*53*). The high ORR is expected to greatly increase the conversion rate of advanced HCC. The authors & facility has conducted a prospective study of conversion therapy with an ICI and a TKI in 33 patients with advanced HCC and an intrahepatic large blood vessel tumor thrombus (*67*). Preliminary results indicated that the ORR was 45.5% (15/33), the DCR was 81.8% (27/33), and the image-based conversion rate was 42.4% (14/33). Ten patients underwent subsequent hepatectomy and had a six-month recurrence-free survival rate of 60.0% during a median follow-up of 11.5 months.

Conversion therapies also present the unique possibility of expanding the population eligible for liver transplantation. Studies on conversion therapies prior to liver transplantation for patients with HCC outside the Milan criteria are still limited and have mixed outcomes (*68-74*). Despite the concern that an ICI might increase the possibility of acute rejection and graft loss in the early post-transplantation period, transplantation can be performed safely with a sufficient washout period between ICI administration and transplantation (*71*). Tabrizian *et al*. reported nine patients undergoing transplantation for HCC after receiving nivolumab at a single center. Severe post-transplant complications were not observed. During the follow-up period, none of the patients developed severe acute rejection or tumor recurrence (*73*). The current author' team has studied a small cohort of six patients with advanced HCC

undergoing a liver transplantation after bridging therapy with an ICI and an AAD. In the cohort, four patients were found to have BCLC-C or China liver cancer (CNLC) stage IIIa cancer; the other two were found to have BCLC-B or CNLC stage IIb. Patients received an average of 5.5 cycles of an ICI (PD-1 inhibitor) and the washout period was 19.5 days prior to transplantation. All of the patients satisfied the liver transplantation criteria after conversion therapy and successfully underwent an orthotopic liver transplantation. All of the patients recovered well without serious complications. None suffered acute rejection or graft loss. The median tumor-free survival was 10.9 months (range 2.9-27.3 months) after follow-up (*70*). Conversion therapy with an ICI and an AAD displayed promise in transplant recipients under close clinical monitoring. However, further research is needed.

Based on domestic practices and discussion among Chinese experts, an expert consensus has been reached (*16*). Inclusion criteria for conversion therapy with an ICI and a TKI for advanced HCC should be: a) CNLC -III/BCLC-C stage HCC; b) Child-Pugh class A liver function; c) an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1; d) 18-75 years of age; e) expected survival of over three months; f) no gastrointestinal bleeding in the past six months; and g) for patients falling outside the inclusion criteria above, preliminary treatment should be performed step by step depending on the specific situation. At the same time, concomitant local treatment may increase the conversion rate and shorten the overall duration of treatment. For patients with extrahepatic metastasis in particular, appropriate approaches are needed to manage extrahepatic lesions. For bone metastases, radiotherapy represents an approach with definite efficacy; for lung metastatic tumors, image-guided radiofrequency ablation might be the treatment of choice.

5. Assessment of conversion therapy

Regular assessment is especially vital after conversion therapy has started. Assessment of conversion therapy mainly includes a general evaluation, the tumor response to conversion therapy, the change in the residual functional liver volume, and serious adverse events.

A general evaluation includes clinical symptoms, as well as the patient's general condition such as mental state, physical status, appetite, and weight, which can be evaluated based on the ECOG-PS score. Imaging evaluation consists of two aspects: tumor response and residual functional liver volume. Evaluation of tumor treatment response is mainly achieved with enhanced magnetic resonance imaging or computed tomography according to the response evaluation criteria in solid tumors (RECIST) or modified RECIST (mRECIST). After treatment takes effect, tumor necrosis occurs first, and absorption is a relatively slow process. Because of the histological and biological change of a necrotic tumor, mRECIST is more suitable for imaging evaluation of conversion therapy. A reduction in tumor diameter can serve as an index with which to evaluate effective treatment, while the disappearance of or decrease in arterial phase enhancement can serve as an imaging feature with which to evaluate the necrosis of a tumor after conversion therapy (Figure 2). In addition, three-dimensional reconstruction could help to precisely analyze the volume change and structural adjacency of a tumor (Figure 3). Positron emission tomography-CT (PET-CT) can assess the treatment response of a primary tumor and extrahepatic metastases. For patients with extrahepatic metastasis, PET-CT has an irreplaceable role in the evaluation of treatment efficacy. Figure 4 presents a patient who underwent conversion therapy followed by subsequent open left-hepatectomy (*75*). After four cycles of combination therapy with an ICI (sintilimab) and an AAD (lenvatinib) for three months, the standard uptake of the tumor decreased significantly, which substantiates obvious tumor necrosis after conversion therapy. One year after the subsequent left-hepatectomy, PET-CT revealed no signs of recurrence.

Assessment of adverse events is mainly based on the patient's chief complaint, combined with an electrocardiogram, chest X-ray film, thyroid function test, routine blood test, myocardial enzymes, and other biochemical indicators. Common adverse events associated with conversion therapy include: a) Skin: skin rash or mucositis; b) Heart: elevated blood pressure or immune myocarditis; c) Digestive tract: nausea, vomiting, diarrhea, or colitis; d) Endocrine abnormalities: thyroiditis, hypothyroidism, or hyperthyroidism; e) Pulmonary: immune pneumonia; f) Kidney: renal insufficiency; and g) Liver: elevated transaminase or abnormal liver function. Most of the adverse events will spontaneously resolve or only need to be treated symptomatically. Combined treatment is rarely interrupted due to adverse events. The principles for adverse event management can be based on the NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities version 2.

When conversion therapy is effective but assessment fails to reveal any further benefit, timely concomitant local therapy or subsequent surgical resection should be performed to eliminate the potential impact of tumor heterogeneity on prognosis. For patients who fail to respond to conversion therapy, second-line approaches need to be taken in accordance with the pattern of tumor progression. Concomitant local therapy or a next-line regimen might be necessary for non-responding or progressive tumors (*11*).

6. Subsequent surgery after conversion therapy

The necessity for subsequent surgery after conversion therapy is mainly determined by: a) A pathological

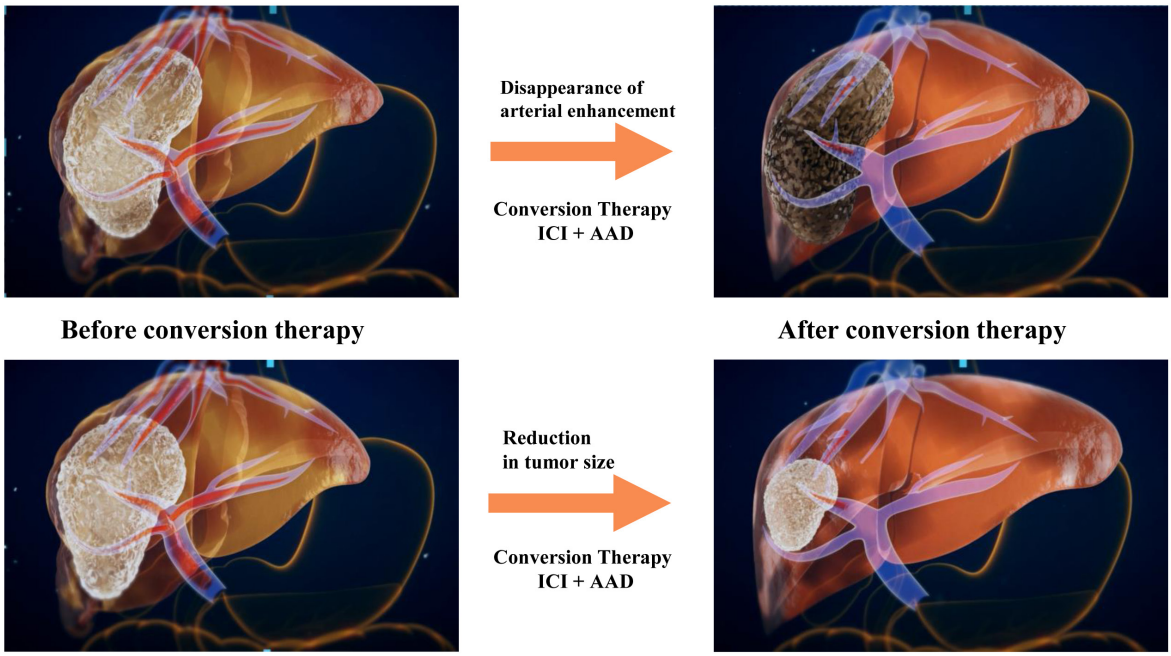

Figure 2. Diagram of Conversion Therapy with an Immune Checkpoint Inhibitor and an Antiangiogenic Drug for Advanced Hepatocellular Carcinoma. The top half of the diagram depicts the disappearance of or decrease in arterial enhancement of the tumor, with shrinkage of a portal or hepatic vein tumor thrombus; the bottom half of the diagram depicts a reduction in tumor size, with shrinkage of the portal or hepatic vein tumor thrombus.

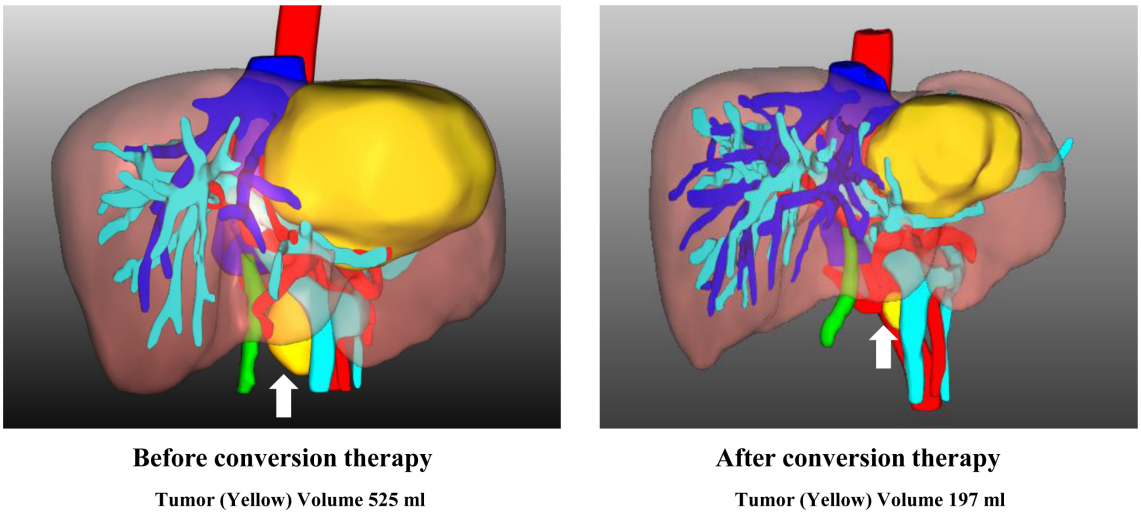

Figure 3. Change in the total tumor volume evident from a 3D reconstruction. A patient in the current conversion cohort. The diagram on the left indicates that the tumor (yellow) volume was 525 mL before combination therapy (a combination of an ICI and an AAD); the diagram on the right indicates that the tumor (yellow) volume was 197 mL after combination therapy (3 cycles of lenvatinib and sintilimab). The white arrow indicates a metastatic lymph node adjacent to the abdominal aorta (lymph node no.16, with increased standard uptake in PET-CT); after combination therapy (3 cycles of lenvatinib and sintilimab), the size and standard uptake according to PET-CT decreased significantly.

examination revealed the efficacy of conversion therapy and guiding postoperative adjuvant treatment, b) Timely surgical intervention to reduce drug resistance and adverse events, c) Complete tumor resection to facilitate radical treatment and ensure a long-term survival benefit. Whether subsequent surgery is indicated in patients in whom a radiological CR has been achieved after conversion therapy is still in question. Studies have indicated that most patients who experienced radiological relief progressed at 12 to 18 months after treatment, even with a continued ICI and AAD (*18,48*). For colorectal liver metastasis, a complete radiological response was achieved in around 60% of resected disappearing liver metastases. If, however, the disappearing lesions remained unresected, then over 50% of the lesions would reappear and recur (*76*). Taken together, most

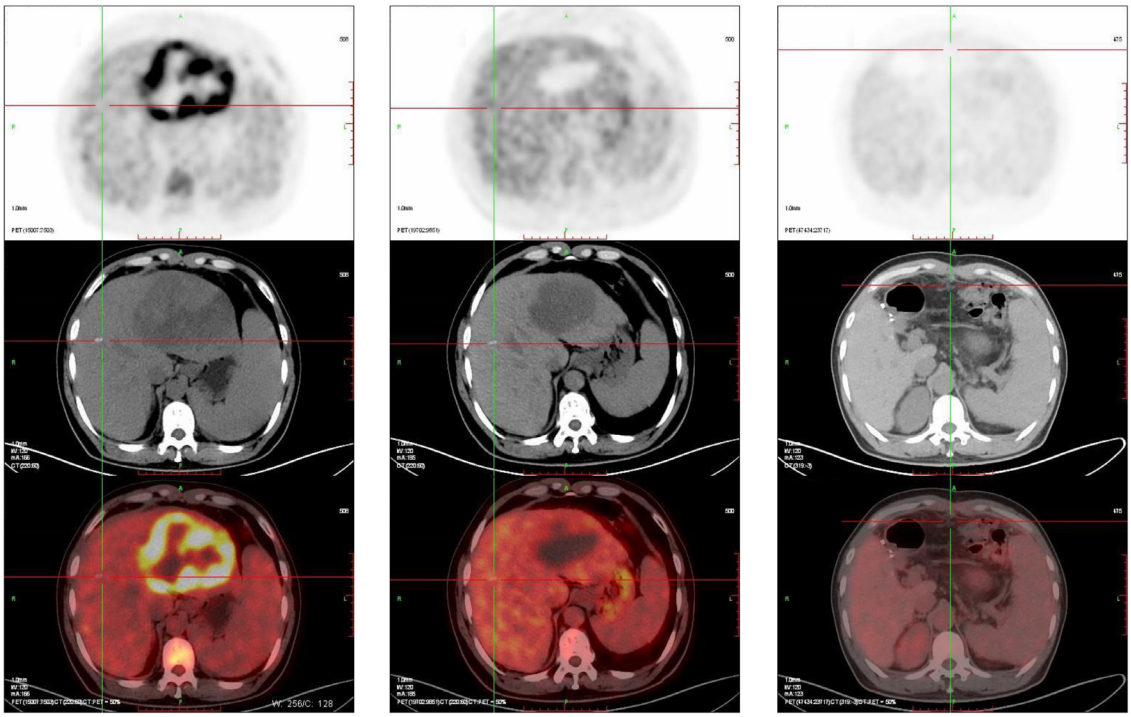

Figure 4. PET-CT assessment of conversion therapy followed by subsequent surgery. A patient in the current cohort who received conversion therapy followed by subsequent open left-hepatectomy. After 4 cycles of combination therapy with an ICI (sintilimab) and an AAD (lenvatinib) for 3 months, the standard uptake of the tumor decreased significantly. One year after subsequent left-hepatectomy, PET-CT revealed no signs of recurrence.

expert consensuses recommend subsequent surgery for patients with a radiological CR after conversion therapy (*16,18*). Nonetheless, more prospective studies need to be conducted to provide more evidence.

Downstaging advanced HCC to CNLC-I stage or BCLC-A stage may be indicated for radical surgery. Technical resectability includes: a) Child-Pugh grade A or B liver function; b) Sufficient residual liver volume, non-cirrhotic patients ≥ 35% standard liver volume, cirrhosis patients ≥ 45% standard liver volume; c) Indocyanine green retention rate at 15 min of < 20%; d) Complete inflow and outflow vasculature; e) Complete biliary structure after surgery; f) ECOG-PS 0~1; g) An American Society of Anesthesiologists Score lower than grade III. Patients who meet the following conditions could also undergo resection or receive local treatment to eliminate tumor heterogeneity: a) Imaging assessment indicates that the tumor has been converted from technically unresectable to technically resectable; b) Extrahepatic metastasis can be resected synchronously; and c) No further tumor response is evident in two consecutive imaging assessments. The timing of surgery remains controversial. Based on the current authors' experience, regular assessment and close management of patients is crucial. In a case series, 41 patients with advanced HCC underwent surgery safely after 3-15 cycles (median five cycle) of conversion therapy; hence, the possibility or timing of subsequent surgery should be assessed after five cycles of an ICI with an AAD (*63*). For patients who are eligible for surgery after conversion, a TKI should be discontinued for seven days and bevacizumab for 28 days before surgery. An ICI can be discontinued at the same time as an AAD (*16*). To prevent tumor progression, the duration of discontinuation should not be too long.

The regimen for postoperative adjuvant therapy remains controversial and mainly requires guidance from a pathological examination of the tumor. Based on discussions among and opinions of domestic experts, preliminary recommendations on post-operative regimens have been formulated. Use of the original conversion therapy regimen for adjuvant therapy after surgery is reasonable, and a consensus recommended that postoperative adjuvant therapy last over six months (*11,18,19*). As a key component in antitumor immunity, memory T-cell recruitment plays a crucial role in long-term maintenance of the antitumor cytotoxic effects of therapy during postoperative immunosurveillance. Continuous postoperative use of an ICI may boost the maintenance of immunosurveillance and immune-clearance against minimal residual disease to reduce the risk of tumor recurrence (*14,77-81*). According to an expert consensus (*11,14,16,82*), if the resected tumor is confirmed to be pathological CR (pCR), preoperative administration of an ICI alone should be continued for six months after surgery. For a tumor confirmed to exhibit a pathological partial response (pPR), the original

conversion regimen should be continued for one year. For pathological progressive disease (pPD), postoperative adjuvant treatment needs to be adjusted depending to the results of a pathological examination and/or genetic testing. The current authors conducted a preliminary study by examining 41 patients with advanced HCC who received conversion therapy and who underwent subsequent surgery from 2018 to 2021 at this facility. These criteria were used to guide post-operative adjuvant therapy. This resulted in a post-operative one-year overall survival rate of 74.7% and a two-year overall survival rate of 60.8%, a one-year recurrence-free survival rate of 56.7% and a two-year recurrence-free survival rate of 48.6%, and a median post-operative recurrence-free survival of 15.9 months (*63*). However, these results are preliminary. Quality evidence and molecular and mechanistic research are still needed to corroborate the recommendations offered here.

Hepatectomy after conversion therapy for advanced HCC is safe and feasible, but more technically demanding (*16,19,63*). An analysis of patients who underwent sequential hepatectomy following conversion therapy indicated that a hepatectomy after conversion therapy resulted in a greater volume of intraoperative blood transfusion, a delayed postoperative recovery, and longer hospitalization than a routine hepatectomy, but the differences were not significant (*16,63,67,75*). A postoperative pathological examination is a crucial indicator of overall survival. Patients with a pathological CR or PR may exhibit significant survival benefits after surgery.

7. Conclusion

The rise of conversion therapy has opened up new avenues for the treatment of advanced HCC. In particular, a combination of an ICI and an AAD has displayed encouraging therapeutic action. Thanks to the combination of an ICI and an AAD or other applicable local treatments, the feasibility of conversion therapy is expected to greatly improve. This will provide more patients with advanced HCC the opportunity to undergo radical surgery and offer them a long-term survival benefit. Moreover, subsequent surgery after conversion therapy with an ICI plus an AAD is a feasible, safe, and promising treatment strategy to prolong long-term outcomes in the population with advanced HCC.

The preliminary results cited herein are encouraging, but certain controversies remain unresolved due to the lack of quality evidence. Hence, more prospective and large-scale studies of conversion therapy and subsequent surgery still need to be conducted.

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Brief Report

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Inclusive education of elementary students with autism spectrum disorders in Shanghai, China: From the teachers' perspective

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SUMMARY Given an increasing number of children with ASD, the need for inclusive education has rapidly increased in China. Since 2011, children with ASD have been eligible for inclusive education. However, little is known of the implementation process by key personnel. The purpose of the current study was to qualitatively explore elementary school teachers' experiences and perspectives on an inclusive education policy and practice for students with ASD. Participants were from 5 elementary schools in 2 districts in Shanghai. This study consisted of data collection in 2 phases. First, semi-structured, in-depth interviews were conducted with school psychologists and vice principals responsible for students' mental health for implementation of general inclusive education at each school. Second, focus groups of frontline teachers were assembled to hear their firsthand experiences. A thematic analysis was performed. Findings indicated that although all 5 schools had some ASD-related support, training and resources varied depending on whether learning in regular classrooms (LRC) was implemented. Frontline teachers in particular faced challenges implementing LRC, including the limited extent of LRC, tedious implementation procedures, and parents' misconceptions of LRC. Regardless of these challenges, frontline teachers tried to support students with ASD as much as they could. The current findings should help to advance the inclusive education policy in Shanghai, including increasing the availability of inclusive education resources and training for teachers, issuing specific LRC guidance, and reducing ASD-related stigma. This study is among the first to explore the implementation of inclusive education in urban China.

Keywords autism spectrum disorder (ASD), elementary school, inclusive education, policy implementation, urban China

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disability characterized by continuing challenges with social communication, restricted interests, and repetitive or stereotyped patterns of behaviors across multiple contexts (*1*). Evidence-based practices are the most useful form of rehabilitation for autistic children, including prompting, differential behavior reinforcement, modeling, naturalistic interventions, and task analysis; these are crucial building blocks of rehabilitation programs for children with ASD (*2*). Many scholars have stressed that these interventions should be provided in natural settings, such as home, community, or school, so that the best functional outcomes of the academic, social, or occupational setting can be achieved (*2*). Inclusive education provides students of all backgrounds the same access to regular classrooms and school environment, which is the basis for implementing evidence-based practices to rehabilitate autistic children in a natural environment (*3*).

In 1994, the United Nations announced the Salamanca Statement proposing inclusive education, advocating that all children be educated in the same educational environment, regardless of whether they had special needs or not (*4*). Since then, countries around the world have explored inclusive education. Previous studies have indicated that receiving an

education in regular schools can help children with ASD improve the interpersonal skills, social adaptability, academic skills, and self-confidence (*5*). Inclusive education in the United States requires placement of the student in the least restrictive environment (LRE), which spans a continuum of placement options from general classrooms to residential school. With various degrees of support from special needs educators, 91.1% of autistic children can eventually be placed in mainstream classrooms (*6*).

Since the 1980s, China has implemented a program of *Sui Ban Jiu Du*, or learning in regular classrooms (LRC), that is focused on including children with special needs in regular classrooms (*7*). In 1988, the first national conference on special needs education affirmed LRC as an official policy of special needs education. In general, LRC provides equal opportunities for children with disabilities to enter regular schools for compulsory education. LRC is open to children with 5 types of disabilities: low vision, hearing loss, a mild intellectual disability, a physical disability, and a mental disability (*8*). The Committee to Certify Disabled Children's Eligibility will examine an enrollment application and make the final decision. According to the "2020 Statistical Bulletin on Education", 49.47% of all students receiving special needs education were included in the LRC program in China (*9*). According to the current inclusive education policy in Shanghai, a school will receive an extra 6,000 RMB (*i.e.*, $941 USD at the current exchange rate) for each student enrolled in the LRC program. A full-time special needs education teacher will be assigned if there are more than 5 students enrolled in the LRC program in each school.

Although the prevalence of ASDs in Chinese children is estimated to be 26.50 per 10,000 (*10*), education of autistic children has been overlooked until the last decade, which is much later than the launch of LRC. In 2006, China classified ASD as a mental disability requiring rehabilitation services (*11*). In 2011, the Chinese Ministry of Education included ASD in the category of a "mental disability", making children with ASD eligible for LRC (*12*). Although the current authors were unable to find specific statistics regarding ASD, *Statistics on Special Needs Education 2020-2021* indicated only 4.62% of all elementary school students enrolled in LRC in China were diagnosed with a mental disability (*13*). In reality, the majority of students with ASD are still excluded from the LRC program for various reasons, including no desire to enroll a child on the part of his or her parents, failing to meet the LRC criteria in practice, a lack of educational resources, or a lack of awareness of the program (*14*).

Even if a child with ASD is successfully placed in a regular classroom, this does not ensure that the child transitions or learns successfully since many receive limited or inappropriate support (*15*). Whether children with ASD continue to successfully operate in a mainstream educational setting depends on many factors. Teacher training is a major challenge of inclusive education. Scholars have contended that better inclusive education training allows special needs teachers to significantly increase their knowledge of ASD and effectively guard against negative attitudes toward inclusive education (*16-18*). However, a lack of teacher training is common around the world (*19-21*). Even in the United States where most ASD students receive inclusive education, their teachers and service providers rarely receive direct and specific training on evidence-based practices for ASD (*19*). Without sufficient ASD-specific training and mentoring, teachers have difficulty understanding each child's characteristics and managing their challenging behaviors. Organizational factors, such as class size and the availability/presence of educational assistants, may further impact students' development of social skills, behavioral management, and social inclusion. Social attitudes also can prevent teachers from creating an inclusive environment (*22-25*).

The school-family partnership is also considered to be an important factor in successful implementation of inclusive education (*26,27*). Teachers and educators strive to establish close collaborative relationships with parents, which is not always successful (*20*). However, the stigma of ASD is another common barrier that prevents families from receiving proper educational and social support for children with ASD. Abnormal/repetitive behaviors, a low level of parental education, ignorance, stereotypes, and misunderstanding of ASD can aggravate the avoidance of inclusive education from the perspective of parents (*28-30*).

Although previous studies have focused on the challenges of inclusive education for students with ASD from the perspective of educators and parents, most used quantitative research methodologies. The literature has remained relatively mute on salient experiences and perspectives of these key personnel during the process of implementing inclusive education, which may shed light on improved policies and practices (*31*). Moreover, existing evidence is primarily from teachers who were already involved in inclusive education. Since students with ASD who are not enrolled in the LRC program have been overlooked in regular Chinese schools, teachers' experiences are understudied. Thus, the purpose of the current study was to use qualitative research methodologies in order to explore teachers' experiences of implementing inclusive education for students with ASD in Shanghai.

2. Materials

2.1. Study setting and procedures

After this study was approved by the Hospital (IRB2021-538), the research team solicited participants

from 10 elementary schools with established teacher-physician collaboration (*e.g.*, fast-track diagnoses and evaluation) in 3 districts in Shanghai. Five schools agreed to participate while the other 5 declined due to time conflicts or privacy concerns. These 5 schools were located in 2 districts in Shanghai, China.

The research team first contacted principals or vice principals who were responsible for managing students' mental health. The purpose of this study and proposed study procedures were explained. Their questions were also answered and their concerns were addressed. The team then met with the school psychologist at each school to obtain information on inclusive education. Once all 5 schools agreed to participate, school psychologists helped recruit frontline teachers, such as head teachers and teachers of main subjects such as Chinese, mathematics, and English, who had direct experience with students with ASD over the past 3 years to participate in focus groups.

2.2. Participants

Four focus groups with 19 frontline teachers were assembled to gain insight from their daily teaching and interaction experiences with students with ASD. Three focus groups consisted of 5 teachers and one consisted of 4 teachers. Eighteen of the participants were female and one was male. These teachers were 38.3 years of age on average and had worked for an average of 16.6 years as elementary school teachers, with years of teaching experience ranging from 3 to 30 years. Six of the teachers were head teachers. The subjects they taught included Chinese, mathematics, English, arts, and music.

Individual semi-structured, in-depth interviews were conducted with 3 vice principals and 4 school psychologists. Six were female and one was male. They were primarily middle-aged, with an average age of 45.1 years. On average, these administrators and school psychologists had relatively extensive teaching experience of 20 years. Participants' demographic information is shown in Tables 1 and 2.

Table 1. Demographic Characteristics of Focus Group Participants (n = 19)

Items	Focus Group Participants
Age (years)	
Average (range)	38.3 (27-51)
25-29	2 (10%)
30-34	5 (26%)
35-39	4 (21%)
40-44	3 (16%)
45-49	2 (11%)
50-54	2 (11%)
Gender	
Female	18 (95%)
Male	1 (5%)
Teaching experience (years)	
Average (range)	16.6 (3-30)
3-5	2 (11%)
6-10	6 (32%)
11-15	1 (5%)
16-20	4 (21%)
21-25	1 (5%)
26-30	5 (26%)
Subject taught	
Chinese	7 (37%)
Mathematics	5 (26%)
English	4 (21%)
Arts	1 (5%)
Music	1 (5%)

Table 2. Demographic Characteristics of Interview Participants (n = 7)

Items	Interview Participants
Age (years)	
Average (range)	45.1 (35-57)
35-39	1 (14%)
40-44	2 (29%)
45-49	3 (43%)
50-59	1 (14%)
Gender	
Female	6 (86%)
Male	1 (14%)
Teaching experience (years)	
Average (range)	20 (6-37)
6-15	3 (43%)
16-25	1 (14%)
26-35	2 (29%)
36-45	1 (14%)

2.3. Data Collection and Analysis

Data collection took place from October to December 2021. All interviews were held in the participants' own offices and focus groups met in the private conference room at each school. Written informed consent was obtained from each participant before data collection. Participants were fully informed that their participation was voluntary and that they could stop whenever they felt uncomfortable or concerned. To protect the anonymity and confidentiality of students and their parents, teachers were asked to use pseudonyms to describe them and not to disclose the students' gender.

All of the interviews and focus groups were conducted in Mandarin. The interviews began with a grand tour question regarding inclusive educational practices at the school. This was followed up with specifics about the daily operation of the LRC program, teacher training, teachers' experiences, and teachers' needs. Each interview concluded with an inquiry about each administrator and school psychologist's suggestions to promote an inclusive education policy and practices in Shanghai. On average, each interview took an hour.

The focus groups began with a question about their general impressions of inclusive education and students with ASD. Teachers were then asked about their understanding of ASD, their daily interactions

with students with ASD, students' parents, their most rewarding and most difficult experiences, pedagogical adaptation, and relevant training. Each focus group concluded with an inquiry about each teacher's suggestions for improving inclusive education. During the focus groups, each teacher was encouraged to participate in the discussion. On average, each focus group took 1.45 hours.

Trained master's students transcribed all of the transcripts into Chinese verbatim. All members of the research team read and open coded all of the transcripts independently. Codes and statements about teachers' experiences with autistic students, inclusive education, interactions with students' parents, as well as teachers' struggles, perceptions, and understanding of inclusive education were identified and extracted from their accounts. With extensive discussion, codes and statements were grouped into various categories based on the similarity of the description (*32*). Themes emerged from recurrent categories of behaviors, expressed feelings, and perceptions (*33*), which were then labeled and defined through extensive discussion. Because the first and second authors are proficient in both Chinese and English, excerpts and themes were translated into English to write up findings. The first and second authors read through the original Chinese transcripts again to ensure that all themes were accounted for. All discussion notes and memos were retained as an audit trail.

3. Results and Discussion

3.1. Current inclusive education practices at a glance

Frontline teachers in the focus groups displayed a surprisingly limited knowledge of the terminology of inclusive education. However, they were familiar with the LRC program and they acknowledged the need for LRC for students with ASD. All 5 schools assigned a vice principal to oversee students' mental health. In contrast to the teachers, these vice principals and school psychologists expressed familiarity with inclusive education and their concerns about its practice in the school, and particularly for students with ASD. One part-time special needs teacher also worked closely with 4 of the schools. Six students had a confirmed ASD diagnosis and dozens more students were suspected of having ASD at the 5 schools, only 2 students with ASD were currently enrolled in the LRC program in 2 schools. In these 2 schools, one had a full-time special needs teacher, and the other had a part-time special needs teacher. Students with ASD enrolled in LRC received a range of support during the learning process to keep up with the regular curricula. For example, Mr. Wang (here, pseudonyms are used for all participants), the vice principal at 1 of the 2 schools, described the details of the LRC program at his school:

> *We evaluate the student's capabilities at the beginning of each school year and create a workbook that monitors the student's progress, including class activity records, interactions with their families, and stratified teaching plans, such as individual sessions or group sessions, for the whole school year. Each teacher of a main subject creates a workbook for each student with ASD. Additional group lessons, individual lessons, and special courses like picture book reading classes are also available.*

The vice principal in the other school, Ms. Jiang, stressed that professional training and guidance for frontline teachers was essential. Her school closely collaborated with the Shanghai Special Education Guidance Center. The Center offers teacher training on LRC techniques for ASD and other types of mental disabilities several times per semester. The Center also evaluates students with ASD each semester in 5 developmental areas, including perception, movement, cognition, speech and communication, and social adaptation.

Teacher training varied among the 5 schools. For the 2 schools that had an LRC program, 12 teachers had received regular training on LRC. A special needs teacher also regularly came to the 2 schools to mentor frontline teachers and school psychologists. In contrast, the other 3 schools had received limited special needs educational support. Although they had attended some form of special needs training before, teachers from these 3 schools had not received any LRC training or undergone regular supervision. For example, Ms. Hu, a school psychologist, mentioned, "I know that there is LRC training, but my school has not participated, perhaps because we currently don't have any students receiving LRC". These 3 schools had not arranged for any stratified teaching at the time of the interviews, either.

3.2. Multifaceted challenges of LRC

Although all teachers agreed that having an LRC program was crucial, tailoring its implementing to the needs of students with ASD was particularly challenging. Teachers identified 3 main areas of challenges, including the limited extent of LRC, tedious LRC implementation procedures, and parents' misconceptions of LRC.

Limited extent of LRC: Although the diagnosis of ASD is listed as a criterion for enrollment in LRC, schools reported that in practice, the intelligence quotient (IQ) < 70 was actually used as the sole enrollment criterion. All of the teachers believed that using IQ as the sole criterion for enrollment in the LRC program was decisively limiting to students with ASD. Students' IQs may differ across the ASD spectrum, so they may all need additional learning support from

the LRC program. Although students with ASD in the 2 schools had an average IQ or above, they still displayed various learning difficulties. For example, Ms. Chen, who was a mathematics teacher with 15 years of teaching experience, remarked, "[The student] had a good memory and was good at calculating, so the student's scores were actually very good in the first grade. Beginning in the third grade, the student had problems with words and difficulty in comprehending sentences. That was a real challenge".

All of the teachers were more concerned about characteristics of ASD that impeded students' participation in regular class activities, such as limited social interaction, not following classroom rules, and behavioral issues. For example, Ms. Qian, another head teacher and an English teacher with 18 years of teaching experience, recalled, "[The student] cried nonstop whenever the teacher assistant (hired by the family) was absent. I think that if [the student] can receive additional emotional support, it could be helpful". Moreover, the question of who to prioritize – students with ASD or the other 40-50 students in the same classroom – was a constant challenge for frontline teachers. All of the teachers expressed their frustration and helplessness. For example, Ms. Sun, who was a Chinese teacher with 30 years of teaching experience, said:

> *The most difficult thing is when anything happens to [a student with ASD] during a class. I don't know whether I should take care of the student [with ASD] first or keep teaching the other students first. I can't take do both at the same time and neglecting either would be unfair.*

This persistent dilemma - taking care of a student with ASD without interrupting regular teaching for other students - was overwhelming to frontline teachers. Thus, teachers believed that the LRC program should cover schooling as a whole, from learning to social interaction, rather than being limited to learning ability in order for students with ASD to be able to participate in regular school life.

Tedious LRC implementation procedures: Implementing the LRC program was a chore for teachers. First, if parents did not report their child's special needs to the school, the frontline teacher was responsible for determining the student's potential eligibility for the LRC program. Without any prior notification of or knowledge on a student's mental health problems, head teachers have to carefully observe each student. All 6 of the head teachers mentioned that they had made such observations during admission interviews, home visits, and daily classroom interactions. Other frontline teachers also mentioned the observations they made during class. When they noticed that something was off, these teachers would report that to the school psychologist and vice principal. The administrators would make a further evaluation. However, these frontline teachers did not use any professional evaluation tools when determining a student's potential LRC eligibility. They admitted that they realized that this could be problematic, but they countered that they had no other professional support except their own teaching experience.

Second, parents' avoidance prevented teachers from suggesting LRC enrollment. For example, Ms. Wu, a head teacher with 21 years of experience of teaching English, stressed, "The biggest problem is no professionals available to suggest LRC directly to parents. Professionals are more persuasive [than teachers]". Currently, the head teacher is responsible for suggest that parents visit a child psychiatrist for further evaluation. Ms. Wu continued:

> *When parents refuse to see a child psychiatrist, the only thing we can do is to wait… wait for the student to get into trouble again and then we can suggest that parents seek medical advice again. It is a long-term battle.*

Only when parents report a student's diagnosis to the school can head teachers follow up by implementing LRC. Teachers were not able to do anything except wait.

Extra paperwork was another reason for the tedious LRC implementation procedures. Almost all of the teachers, and especially head teachers, considered the extra paperwork to implement the LRC program as "unrealistic" for each student with ASD. For example, Ms. Zhou, a head teacher who taught Chinese for over 27 years, said, "I agree that the LRC program can be very helpful, but considering all the paperwork and procedures I have to go through, I'd say 'No.'" In fact, all of the teachers believed that their everyday teaching and mentoring of students with ASD already exemplified the concept of LRC. Ms. Zhou continued:

> *We really care about this student and we have helped [this student] make significant progress. Honestly, what we have done is equivalent to LRC. I'd rather keep on doing the one-on-one tutoring after school than fill out a whole lot of paperwork.*

What was worse, teachers were not been properly compensated for their efforts to meet the learning needs of students with ASD. When one student is enrolled in the LRC program, the head teacher and teachers of Chinese, Mathematics, and English can receive a subsidy, ranging from 30 RMB to 500 RMB each month (*i.e.*, $4.7-$78.5 USD at the current exchange rate). As such, the existing heavy workload and inequivalent compensation for the LRC program further diminish teachers' motivation to implement the LRC program.

Parents' misconceptions of LRC: Teachers believed that parents' avoidance was related to

their misconceptions of LRC, which stemmed from stigmatization of intellectual disabilities and ASD. LRC eligibility depends on IQ, so parents refused to have their children be considered "developmentally challenged". For example, Ms. Feng, who had taught mathematics for over a decade, said, "A mother was afraid that her child would be considered retarded after signing up for LRC even though she knew that her child was in need". Teachers understood parents' concerns but still valued the benefits of LRC.

Still, teachers were frustrated that most parents chose to ignore their children's ASD-related symptoms. For example, Ms. Jin, who had taught English for 15 years, recalled, "When I was a head teacher, a father refused to discuss with me his child's repetitive behaviors in the classroom. He just believed that his child was going to grow out of it…". The stigma of ASD, mental health, and intellectual disabilities prompted parents to not disclose any information about their child's mental health problems, let alone a diagnosis of ASD. Ms. Jin continued, "A mother was reluctant to let me praise her child's progress at the parent-teacher meeting. She believed such public acknowledgement would actually expose her child's condition". Even when a few parents had chosen to seek professional help and disclosed their children's diagnosis to the school, they were still likely to forego the LRC program. The stigma related to the LRC prompted parents to turn away from inclusive education.

3.3. Inclusive education in practice

In reality, all of the teachers, including vice principals and frontline teachers, agreed that a variety of practices embodying inclusive education had already been integrated into routine teaching, regardless of whether LRC had been implemented or not. All teachers felt that they were responsible for doing their best to help students with ASD. Head teachers often asked for help from colleagues, school psychologists, and administrators. Teachers of different subjects shared strategies that worked for individual students with ASD to better facilitate the learning process for these students. Many teachers also gained ASD-related knowledge on their own time. Moreover, teachers tried to meet the needs of students with ASD as much as possible. During class, they tried various strategies, such as comforting, incentives, paying more attention, time-outs, and ignoring minor misbehavior. Head teachers also arranged for other students to be desk mates to help students with ASD study and interact socially.

Teachers and school administrators also actively sought to collaborate with students' parents. Teachers tried to invite parents to accompany their children as a private tutor in the classroom, and especially when parents received relevant rehabilitation training. For example, Ms. Bai, who taught mathematics for just 3 years and who was often nervous about classroom order, said, "When the parent was present, I felt quite relieved". The schools had also invited parents to attend workshops on parenting skills.

This study is among the first to explore the experiences and perceptions of school administrators and frontline teachers with regard to inclusive education in urban China. Inclusive education emerged in the US in 1975, but LRC appeared for the first time in China in 1987, and the inclusion of ASD students was not stipulated until 2011 (*12*). Despite its nascent stage, inclusive education, and LRC in particular, has been well received in Shanghai. Although not all frontline teachers were familiar with the terminology of inclusive education, the concept LRC was not unfamiliar to them. All frontline teachers felt a sense of responsibility to help students with ASD adapt to regular classroom teaching as much as they could, regardless of whether LRC was implemented. None of the participants rejected or avoided students with ASD. This finding is contrary to the results of previous studies, which found that teachers were undecided or they displayed negative attitudes towards inclusive education (*34,35*). However, frontline teachers acknowledged difficulties with the actual implementation of LRC, including its tedious procedures, limited extent, and parents' misconceptions. These difficulties further exacerbated the already undermet needs of students with ASD. More individualized educational programs are needed to cater to each autistic student's needs (*6,36*).

The current findings should help to advance the inclusive education policy in Shanghai. First, increasing the availability of inclusive and/or special needs educational resources and training for teachers is crucial. Findings indicated that relevant resources primarily depend on the current number of students enrolled in the LRC program in Shanghai. When no students are currently enrolled in LRC at a school, special needs educational support is likely to stop. This finding is consistent with existing evidence that teacher training is often in short supply in many countries (*37,38*). The lack of relevant training has been found to cause stress for a large number of teachers (*39*), which likely triggers burnout (*40*). Thus, relevant training in inclusive education should be available to all teachers in all mainstream schools. Training can enhance teachers' knowledge and self-efficacy, which is essential to interventions for students with ASD (*41*). Consistent with previous findings (*42,43*), the current participants also believed that ongoing professional development, such as curriculum design and stratified syllabus preparation, is key to successful LRC implementation.

A related topic is the need to balance special needs education resources among schools citywide. Two schools with students currently in the LRC program reported their close collaboration with the Shanghai Special Education Guidance Center but the other 3 did

not. Nevertheless, all 5 of the participating schools had established a teacher-physician collaboration for fast-track diagnosis and evaluation of students' mental health problems. Such collaboration should occur at every elementary school in Shanghai to aid frontline teachers and parents (*44*). Hiring teacher assistants or specialized agencies, which are widely used in developed countries, is another possible solution to fill the gap of limited professional personnel (*45*).

Second, specific LRC guidance for students with ASD in Shanghai needs to be issued. First, ASD is listed under the category of a "mental disability" in the inclusive education policy, which accounts for parents' strong resistance. The word "mental disability" is often connected to "crazy", "out of control", and "attack" in Chinese culture (*46*), which may lead to parents' concerns about social exclusion and even the expulsion of their children from regular schools. Second, there is no specific guidance for enrollment of students with ASD students in the LRC program. As an example, there are no detailed rules for reference for specific educational placement, teaching plans, or evaluation of students with ASD for the LRC program. Parents have difficulty monitoring the LRC program and their children's academic and social progress. Thus, even when teachers recommend the LRC program, parents may still eschew it.

Compared to a "mental disability", an intellectual disability is a more approachable alternative for schools and has become a substitute criterion for LRC enrollment. According to *Statistics on Special Needs Education 2020-2021*, the diagnosis of an intellectual disability is 8 times higher than that of a mental disability among elementary school students enrolled in LRC (*13*). Given the spectrum nature of ASD, the cognitive capacity of each student can vary significantly. Under the current criteria, many students with ASD and a normal IQ but impaired social skills are not eligible for LRC, which precludes teachers and schools from paying special attention to these children. For these reasons, ASD should be considered as an independent special needs education category in order to address these practical issues and help both students and their parents and teachers. This practice has already been in effect in other places, such as Japan, Taiwan, and the United States (*47-49*). In Shanghai, LRC eligibility is being experimentally expanded to include other neurodevelopmental disabilities, such as attention deficit/hyperactivity disorder (ADHD) and learning disorders. The same should be done for ASD.

Finally, the deeply-rooted stigma of mental disorders that hinders families actively seeking diagnose and accepting the concept of inclusive education needs to be acknowledged (*28*). Asian culture usually focuses on children's academic performance instead of prioritizing social and emotional aspects. Since *China's 2035 Education Modernization* plan was published in 2019 (*50*), a comprehensive development framework that values children's mental health has increasingly been favored by the public. The recently announced "ease the burden of excessive homework and off-campus tutoring for students receiving compulsory education" ("*Shuang Jian*") policy can also help to promote education equality for students with ASD. The services the government can provide and how to actively access resources should be publicized to encourage greater involvement of families of children with ASD.

Limitations: This study's limitations should be kept in mind when interpreting the current findings. First, the sample size was relatively small. Tight teaching schedules prevented more teachers from participating in the study than planned. More ASD-related characteristics would have been included if more teachers participated. Second, the 5 schools in this study had partnerships with this Hospital. Teachers from other schools lacking teacher-physician collaboration may have different experiences. Third, the findings may not generalizable nationwide. This study was conducted in Shanghai, which is one of the most economically developed cities in China. A point worth mentioning is that the sample was only from 2 districts in Shanghai, which may not represent LRC implementation and inclusive education at all elementary schools. Finally, this study focused only on elementary school. Future research on students with ASD should cover the 9 years of compulsory education.

In conclusion, it takes a village to care for students with ASD. This study is an important first step to understanding an inclusive education policy that includes ASD and its implementation in urban China. Findings suggested that elementary school teachers in Shanghai are receptive to including students with ASD. Findings also revealed the current challenges of implementing inclusive education and an LRC program in Shanghai, and corresponding suggestions have been offered. Future research should examine special needs educational resources and implementation in other areas of China in more detail.

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Brief Report

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Time to onset of drug-induced parkinsonism: Analysis using a large Japanese adverse event self-reporting database

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SUMMARY Whether there are differences in the time to onset of drug-induced parkinsonism (DIP) depending on the type of drugs causing DIP remains uncertain, so that question was investigated here using a large real-world database. Fourteen DIP-related drug categories were defined to perform a disproportionality analysis using a large Japanese pharmacovigilance database containing more than 600,000 self-reported adverse events (AEs) recorded between April 2004 and September 2021 to identify AEs indicating "parkinsonism" in association with the defined drug categories. The time from drug administration to the onset of DIP was comparatively analyzed. Results indicated that the median time to onset was shorter than 1 month in more than half of the cases of DIP; it was shortest with peripheral dopamine antagonists (median: 0.1 weeks), followed by benzodiazepine (median: 0.5 weeks), butyrophenone (median: 0.7 weeks), novel antidepressants (median: 2.5 weeks), atypical antipsychotics (median: 3.3 weeks), other antidepressants (*e.g.*, lithium, median: 3.7 weeks), and benzamide (median: 4.5 weeks). In contrast, anti-dementia drugs, tricyclic antidepressants, and antiepileptic drugs resulted in a relatively longer time to onset (median: 9.9, 17.2, and 28.4 weeks, respectively). In addition, a maximum delay of even longer than 2 years was reported for benzamide (846 weeks), anti-Parkinsonism drugs (382 weeks), phenothiazine (232 weeks), atypical antipsychotics (167 weeks), anti-dementia drugs (161 weeks), and benzodiazepines (120 weeks). The current results suggested that the characteristics of the time to onset of DIP may substantially differ depending on the type of drug causing that DIP. This finding may help when diagnosing patients with parkinsonism.

Keywords drug-induced parkinsonism, real-world data, adverse events, pharmacovigilance

1. Introduction

Drug-induced parkinsonism (DIP) is a syndrome in which parkinsonian symptoms typically occur within a few months after receiving specific drugs (*1,2*), such as antipsychotics (*3*). Parkinson's disease (PD) is characterized by a faster clinical course, a higher frequency of a symmetrical distribution of symptoms, or a poorer response to levodopa therapy. Although dopamine antagonists are drugs that typically cause DIP (*1,2*), it can also be caused by various types of medications, including antidepressants (tricyclic antidepressants [TCAs], novel antidepressants, including selective serotonin reuptake inhibitors [SSRIs]), benzodiazepines, calcium channel blockers (CCBs), peripheral dopamine antagonists (metoclopramide or domperidone), antiepileptic drugs (valproate), or other miscellaneous drugs (*4*).

When diagnosing DIP, physicians suspect the drug that a patient recently started taking is the cause of acute-onset parkinsonian symptoms, so the drug is withdrawn to confirm the diagnosis of DIP. This is because the time from administration to the development of DIP is, in many cases, short. An earlier pharmacovigilance study based on a large number of self-reports from France (*4*) reported that approximately 70% of cases of DIP occurred within 3 months after receiving the drugs that caused DIP. An earlier study also reported that 20% of cases of DIP occurred up to 12 months after administration (*4*). CCBs were also reported to result in a longer time to onset than typical antipsychotics or benzamides (*4*). This means that the duration of the time to onset may need to be considered in order to correctly differentiate DIP from PD and to

identify the drug causing DIP. This is because DIP and subclinical dopaminergic dysfunction sometimes occur concurrently (*2,5*) and because patients with DIP are sometimes taking several types of potentially causative drugs simultaneously (*e.g.*, CCBs for hypertension and antidepressants for depression). To date, however, the details of the time to onset due to other potentially causative drugs or possibly a longer range of time remain unclear. If these details can be characterized in detail, then this might help clinicians determine the likelihood of a drug being the cause of their patients' parkinsonism.

To address these points, potential cases of DIP were analyzed using a large Japanese database of self-reported adverse events (AEs). This pharmacovigilance database provides structured data on a large number of cases of potentially drug-induced AEs, including dates of drug administration and AE onset. Despite its limitations due to the nature of self-reports, this database has been widely used to identify hypothetical associations between drugs and AEs (*6*). The current attempt might provide some useful suggestions regarding more detailed aspects of time to onset that are difficult to collect in sufficient numbers in conventional observational studies.

2. Materials and Methods

2.1. Data acquisition and preprocessing

This was a retrospective pharmacovigilance study using the Japanese Adverse Drug Event Report (JADER) database provided by the Pharmaceuticals and Medical Devices Agency (PMDA). Data were downloaded with permission from the PMDA website (*https://www.pmda.go.jp*) on December 2021, and they included more than 600,000 case reports with potential drug AEs recorded in Japan between April 2004 and September 2021. The JADER database consists of 4 component data tables (*6,7*): [1] "demo", which provides each unique case IDs, sex, age group (*e.g.*, 40s or 60s), year of the report, route of the report (*e.g.*, from a clinical trial or spontaneous reporting), and reporters' demographics (*e.g.*, medical doctor, pharmacist, lawyer, consumer); [2] "reac", which includes all adverse reactions potentially due to drug use for each patient; [3] "drug", which includes all possibly associated drugs, their dose, indications for their usage, and the date of administration and discontinuation; and [4] "hist", which includes each patient's primary illness or medical history. In the "drug" table, the extent to which a drug is suspected of causing an AE is classified as "suspected", "concomitant", or "interacting". The current analysis included only the "suspected" drug category to reduce the number of false-positive cases in order to obtain sufficient specificity of the reported DIP with respect to true DIP. The types of reporters to the database were limited to doctors, pharmacists, or any other medical staff but excluded lawyers or consumers to increase the diagnostic certainty of the reported DIP. The report's quality, evaluated in accordance with the World Health Organization criteria (*8*), was also examined, and reports of poor quality (*i.e.*, grade = 0) were excluded from the analysis. Duplicate AEs in the "reac" table reported for the same case ID or duplicate drug names in the "drug" table reported for the same case ID were subsequently deleted.

Since the JADER database infrequently contains potentially duplicate records for the same patient but reported by different reporters (*e.g.*, by the hospital doctor and the pharmaceutical company) with different case IDs, reported AEs in the "reac" table were excluded when all of the following data matched completely: the AE, outcome, date of AE onset, age group, sex, weight, height, year of the report, and quarter of the report (Q1-Q4). Moreover, reported drug information records in the "drug" table were excluded when all of the following data matched completely: drug name, date of drug administration and discontinuation, age group, sex, weight, height, year of the report, and quarter of the report (Q1-Q4).

2.2. Database search

In the JADER database, AEs and disease indications are given by the Preferred Terms determined by the Medical Dictionary for Regulatory Activities/Japanese version (version 22; *https://www.pmrj.jp/jmo/php/indexe.php*). Here, the term "Parkinsonism" (level, PT) alone was used for the search, and patients presenting with this AE were deemed to have DIP. Other terms related to PD symptoms (*e.g.*, "Resting tremor", "Rigidity", "Akinesia", or "Postural instability") were not included as criteria for DIP in order to obtain greater specificity for a parkinsonian diagnosis.

Suspected drugs in these cases of DIP were identified. Fourteen drug categories were arbitrarily defined in accordance with the literature (*1,2,4*), as listed in Table 1. Table 1 also provides the corresponding drug names actually identified in the database, including the following: antipsychotic types (including categories of phenothiazine, butyrophenone, benzamide, and atypical antipsychotics); peripheral dopamine antagonists; antidepressants (including categories of tricyclic/tetracyclic antidepressants, SSRI, serotonin and noradrenaline reuptake inhibitors [SNRIs], noradrenergic and specific serotonergic antidepressants [NaSSAs], and other antidepressants); hypnotic drugs, including benzodiazepine or non-benzodiazepine categories; and other types of drugs, including categories of antiepileptic drugs, anti-dementia drugs, anti-PD drugs, CCBs, and histamine blockers. Any miscellaneous drugs not included in these categories are not shown in the table.

Cases in which parkinsonism was present before the use of the drug were excluded, and then each reported case was classified (*9,10*) depending on binomial factors:

Table 1. List of the 14 drug categories and the corresponding drug names identified from the database

Drug category	*n*	Included drugs
Phenothiazine	13	Chlorpromazine (*n* = 6), prochlorperazine (*n* = 3), levomepromazine (*n* = 1), perphenazine (*n* = 1), fluphenazine decanoate (*n* = 2)
Butyrophenone	10	Haloperidol (*n* = 10)
Benzamide	22	Sulpiride (*n* = 18)
Atypical antipsychotics	85	Risperidone (*n* = 17), aripiprazole (*n* = 22), olanzapine (*n* = 4), quetiapine (*n* = 8), paliperidone (*n* = 11), perospirone (*n* = 5), blonanserin (*n* = 5), clozapine (*n* = 8), asenapine (*n* = 5)
Peripheral dopamine antagonist	9	Metoclopramide (*n* = 8), domperidone (*n* = 1)
Tricyclic antidepressants	4	Amoxapine (*n* = 2), mianserin (*n* = 1), amitriptyline (*n* = 1)
Novel antidepressants (SSRI, SNRI, NaSSA)	24	Paroxetine (*n* = 8), mirtazapine (*n* = 4), sertraline (*n* = 1), duloxetine (*n* = 3), escitalopram (*n* = 3), fluvoxamine (*n* = 2), milnacipran (*n* = 2), venlafaxine (*n* = 1)
Other antidepressants	5	Lithium carbonate (*n* = 1), trazodone (*n* = 4)
Benzodiazepines	14	Etizolam (*n* = 4), clonazepam (*n* = 4), flunitrazepam (*n* = 3), lorazepam (*n* = 1), bromazepam (*n* = 2)
Antiepileptic drugs	5	Valproate (*n* = 3), carbamazepine (*n* = 1), levetiracetam (*n* = 1)
Anti-dementia drugs	19	Donepezil (*n* = 7), galantamine (*n* = 5), memantine (*n* = 4), rivastigmine (*n* = 3)
Anti-Parkinson drugs	9	Levodopa (*n* = 2), pramipexole (*n* = 2), biperiden (*n* = 3), amantadine (*n* = 2)
Calcium channel blockers	2	Amlodipine (*n* = 1), nicardipine (*n* = 1)
H_2 antagonists	2	Famotidine (*n* = 1), lafutidine (*n* = 1)

Parentheses indicate the number of patients with drug-induced parkinsonism and the exposure to each drug (or drug category). Other miscellaneous drugs not included in the above categories are not considered. *Abbreviations*: SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant.

with/without exposure to the drug category of interest as listed above and with/without the occurrence of an AE involving parkinsonism, regardless of the timing of drug administration or occurrence of an AE.

2.3. Statistical analyses

All statistical analyses were performed using the software R (version 3.6.3). For each included drug, the reporting odds ratio (ROR) was calculated to identify drugs potentially associated with the development of DIP. The (crude) ROR was calculated using a two-by-two contingency table (*9,10*), where all reports were classified using two factors: with/without DIP and with/without exposure to each drug category. When the lower 95% confidence interval (CI) of the ROR was greater than 1, the DIP was significantly reported more often following the use of the drug category of interest than after the use of all other drugs/drug categories.

Next, a time-to-onset analysis was performed. The period (in weeks) after administration of the drug to the onset of DIP was considered to be the disease-free survival, and the Kaplan-Meier method was used to calculate an estimated survival curve. The drug categories with sufficient cases were selected for further statistical analysis. The 50% survival and its 95% CI were calculated using the R package *survival*. In addition, survival was compared between two drug categories using the Gehan-Wilcoxon test. *P*-values from multiple Gehan-Wilcoxon tests were adjusted using the Benjamini-Hochberg (BH) method for multiple comparisons.

2.4. Ethics

This study was approved by the Institutional Ethics Committee of the University of Tokyo Graduate School of Medicine (ID: 11628-[3]). Informed consent was not required for this type of study because this study only used publicly distributed data. This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

3. Results and Discussion

In total, 392,835 AEs were reported within the period studied. There were 311 reported cases (0.08%) of DIP. More than half of the patients with DIP were women (172/311, 55.3%), and their median age group was 60-69 years (interquartile range: 50-70 years). Atypical antipsychotics were the most frequent drug category taken by patients with DIP (85/311, 27.3%), followed

Table 2. Detailed summary of the 14 drug categories

Drug category	*n*	Crude ROR (95% CI)		Medication to onset (weeks)		
				Median (95% CI)	Minimum	Maximum
Phenothiazine	13	23.98 (14.55 - 37.5)	*	5.70 (2.1 - NA)	0.1	232.1
Butyrophenone	10	33.08 (19.23 - 53.72)	*	0.70 (0.3 - NA)	0.1	56
Benzamide	22	100.25 (72.01 - 137.55)	*	4.05 (1.4 - 12.1)	0.1	846
Atypical antipsychotics	85	23.29 (18.21 - 29.64)	*	3.30 (2 - 5.7)	0	166.9
Peripheral dopamine antagonists	9	25.57 (14.04 - 43.1)	*	0.10 (0.1 - NA)	0	95.9
Tricyclic antidepressants	4	14.12 (6.01 - 28.33)	*	17.15 (2.7 - NA)	2.7	19.3
Novel antidepressants (SSRIs, SNRIs, NaSSAs)	24	11.15 (7.84 - 15.5)	*	2.45 (1.3 - 5.6)	0.1	115
Other antidepressants	5	17.68 (9 - 31.55)	*	3.70 (0.9 - NA)	0.9	6.6
Benzodiazepines	14	7.23 (4.22 - 11.66)	*	0.50 (0 - 43.1)	0	120.3
Antiepileptic drugs	5	1.21 (0.48 - 2.52)		28.40 (11.4 - NA)	5	258.1
Anti-dementia drugs	19	15.54 (10.12 - 23.01)	*	9.90 (6.4 - 40.1)	0.3	160.6
Anti-Parkinson drugs	9	11.30 (6.36 - 18.71)	*	9.10 (4 - NA)	1.4	382
Calcium channel blockers	2	6.96 (3.43 - 12.67)	*	0.75 (0.4 - NA)	0.4	1.1
H_2 antagonists	2	1.98 (0.54 - 5.14)		18.4 0(0.9 - NA)	0.9	35.9

*, Significantly elevated ROR (lower 95% CI > 1). The median and 95% confidence interval (CI) of the time to onset were obtained *via* a survival analysis. When the number of reported cases was insufficient, the 95% CI could not be adequately determined. In such instances, the upper limit of the 95% CI is marked N/A. Abbreviations: DIP, drug-induced parkinsonism; ROR, reporting odds ratio; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressants; N/A, not available.

by novel antidepressants (24/311, 7.7%) and benzamide (22/311, 7.1%).

A detailed summary of the results for the 14 drug categories is shown in Table 2. Most of the drug categories were significantly reported more often for DIP (as shown with an asterisk (*), meaning that the lower limit of the 95% CI was > 1). This was especially true of benzamide (*e.g.*, sulpiride). Figure 1A shows the median time to onset of DIP for each of the 14 drug categories (excluding those with significantly few cases [$n < 3$]) arranged in order of their medians. The boxes for the drug categories with a sample size large enough to determine the 50% survival and 95% CI are colored in gray (Figure 1A). The number of eligible patients in each drug category and the disease-free survival varied substantially depending on the drug category.

The median disease-free survival was shorter than 1 month in more than half of patients with DIP (50% of the disease-free survival for all patients with DIP was 28.0 days). This was shortest in patients administered peripheral dopamine antagonists (median: 0.1 weeks), followed by benzodiazepine (median: 0.5 weeks), butyrophenone (median: 0.7 weeks), novel antidepressants (median: 2.5 weeks), atypical antipsychotics (median: 3.3 weeks), other antidepressants (*e.g.*, lithium, median: 3.7 weeks), and benzamide (median: 4.5 weeks). In contrast, anti-dementia drugs resulted in a relatively long disease-free survival (median: 9.9 weeks). Patients administered TCAs or antiepileptic drugs had a significantly longer disease-free survival (median: 17.2 and 28.4 weeks, respectively), but their limited sample size decreased the reliability of those numbers.

Considering the maximum disease-free survival, the maximum delay of more than 2 years was reported for benzamide (846 weeks), anti-PD drugs (382 weeks), phenothiazine (232 weeks), atypical antipsychotics (167 weeks), anti-dementia drugs (161 weeks), and benzodiazepines (120 weeks). Moreover, the minimum disease-free survival was < 1 week in many drug categories, although antiepileptic drugs resulted in a minimum disease-free survival of > 1 month.

Five drug categories had a sufficient number of reported cases to determine the 50% survival and its 95% CI (boxplots in gray in Figure 1A): benzodiazepine novel antidepressants (*i.e.*, SSRI, SNRI, and NaSSA), atypical antipsychotics, benzamide, and anti-dementia drugs. The disease-free survival was compared among these five drug categories. Among the 10 pairs in the Gehan-Wilcoxon test, anti-dementia drugs versus novel antidepressants (corrected $p = 0.044$), anti-dementia drugs versus atypical antipsychotics (corrected $p = 0.044$), and anti-dementia drugs versus benzamide (corrected $p = 0.023$) resulted in significant differences in disease-free survival. Survival curves in Figure 1B reveal a longer disease-free survival distribution for anti-dementia drugs.

This study investigated reports of parkinsonism as a potential drug-induced AE along with the administration of several causative drug categories. Results indicated that most of the defined drug categories resulted in DIP significantly more often. Moreover, they resulted in varied median disease-free survival and maximum disease-free survival of varying lengths, which were as long as 2-16 years. The minimum disease-free survival was less than 1 week. These results suggest that the disease-free survival may substantially differ depending on the type of drugs causing DIP. This finding may help to inform clinical practice when diagnosing patients with parkinsonism.

The clinical utility of the current study is particularly

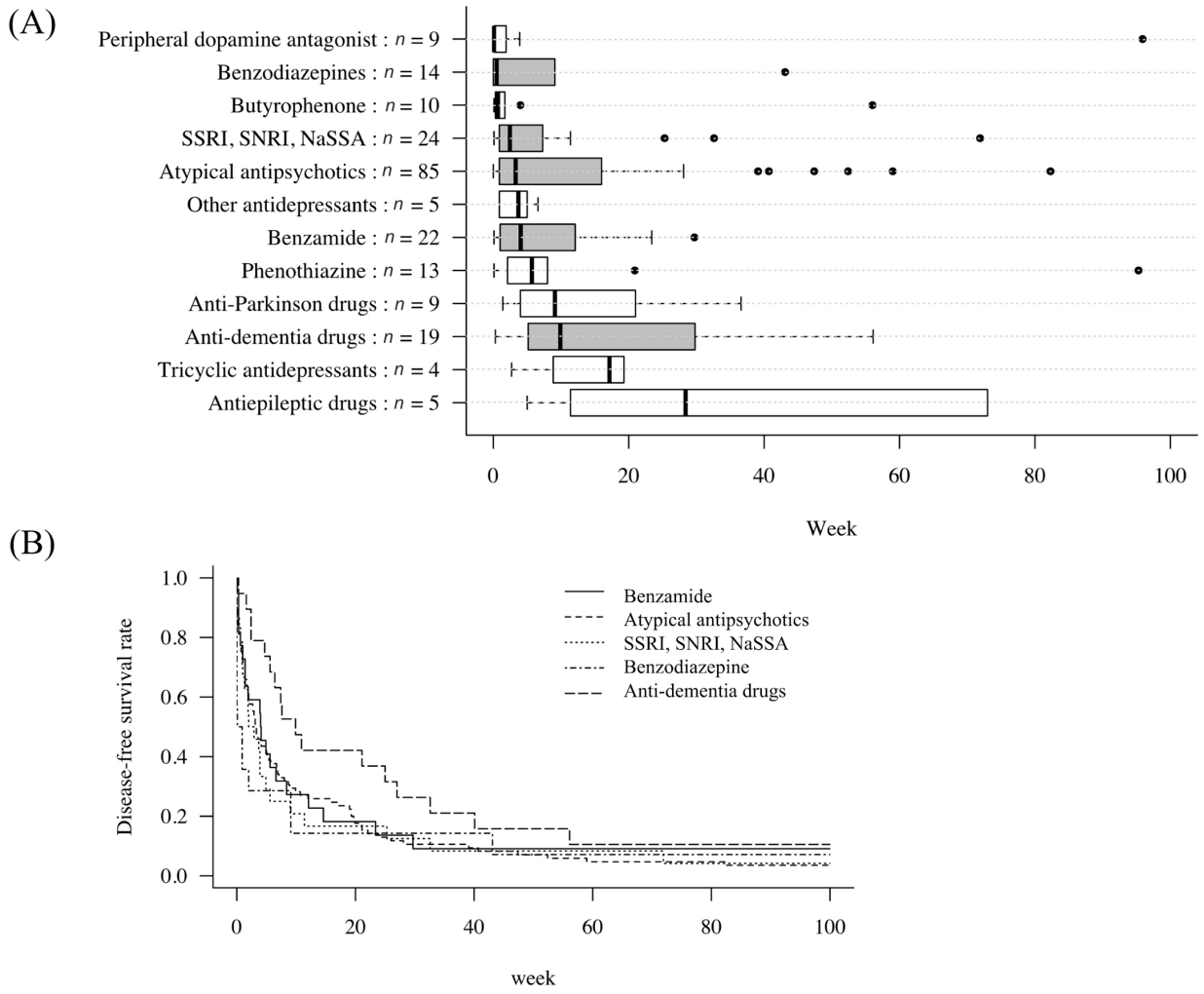

Figure 1. Summary of the disease-free survival in each drug category. The period of onset for the 16 drug categories is summarized as boxplots **(A)**, in order of median time. Cells in a category with a sample size large enough to determine the 50% survival and its 95% confidence interval are colored gray. **(B)** Survival curves from the administration of benzodiazepines or anti-dementia drugs to the onset of drug-induced parkinsonism (DIP). Anti-dementia drugs resulted in a significantly longer disease-free survival than atypical antipsychotics ($p = 0.040$, corrected using the Benjamini-Hochberg [BH] method), selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and noradrenergic and specific serotonergic antidepressants ($p = 0.040$, corrected using the BH method), but no other drug pairs resulted in significant differences in survival.

evident in several specific clinical scenarios as follows (here, etizolam is used as an example of a drug with a short delay and donepezil as a drug with a long delay):

i) When one patient with acute-onset parkinsonism was administered etizolam 1 week before onset and donepezil 1 year before onset, both should be considered potential causes of parkinsonism.

ii) When one patient exhibited parkinsonism soon after donepezil was administered for dementia, donepezil should not be ruled out as the potential cause of parkinsonism, regardless of its long disease-free survival.

iii) In one patient with acute-onset parkinsonism and a long (2 years) concurrent history of taking etizolam, the possibility that DIP was due to etizolam cannot be immediately discounted.

iv) When one patient with acute-onset parkinsonism was administered both etizolam and donepezil 1 week before onset, etizolam would more likely be the cause of parkinsonism based on its disease-free survival.

The major strength of the current study is its use of the JADER database. DIP is not a frequent disease, with an annual incidence of 3.3 per 100,000 person-years in 1976-2005 in the United States (*11*) and an estimated incidence of 7.1 per 100,000 person-years in 2012 in South Korea (*12*). Thus, collecting a sufficient number of cases of DIP to conduct an observational study of a large enough scale is not always easy. The self-reporting pharmacovigilance database features reports from a large number of Japanese patients in the real world, allowing a review of a sufficient number of reports that would be difficult in earlier observational studies.

The basic characteristics of the cases of DIP identified in the current study were generally consistent with an earlier pharmacovigilance study from France summarizing reports from 1993 to 2009 (*4*), where approximately half of the patients with DIP were in

their 60s and 70s, and 60% of all patients with DIP were women. The frequency of DIP in that study was 0.7%, which was higher than that in the current study (0.080%), and whether the frequency of DIP differed among all of the self-reported cases examined is uncertain. DIP is defined as the presentation of at least one PD symptom (*i.e.*, resting tremor, rigidity, and akinesia), whereas the current study defined DIP as having "parkinsonism" alone. However, this difference in the definition of DIP alone cannot explain the difference in frequency because the frequency of DIP in the JADER database increased to 0.12% when a definition like that used in the earlier study was used. In addition, the higher frequency of atypical antipsychotics reported in the current study (27.3%, 85/311) also differed from the lower frequency reported in the earlier study (13.5%, 21/155). The increased use of atypical antipsychotics and the decreased use of conventional antipsychotics over time since the 1990s (*13*) may partly explain the fewer reports of DIP since the data analyzed here included cases reported from 2004-2021, about a decade more recent than the earlier study (*4*).

Varied median time to onset may reflect the different underlying mechanisms of the parkinsonism observed. Dopamine antagonists, antidepressants, or benzodiazepines directly inhibit the dopaminergic pathway. Thus, they can induce parkinsonism with a relatively short delay. The reason DIP was reported as an AE after using anti-PD drugs, which should relieve parkinsonism symptoms by themselves, is still unclear. Presumably, these reports represented a spurious correlation confounded by the underlying Lewy body pathology: these "reported" cases may have actually been the prodromal phase (*14*) or paradoxical worsening (*15*) of the underlying PD or patients with dementia with Lewy bodies.

Antiepileptic drugs also resulted in a longer disease-free survival, and the mechanism for this remains unclear. Although infrequent, valproate causes parkinsonism (*5,17*). An earlier review discussed several possible mechanisms of valproate-induced parkinsonism (*18*), such as altered neurotransmitter signaling *via* its GABAergic effect, altered gene expression by activating extracellular-regulated kinase activity, or the unmasking of subclinical dopaminergic deficits by these mechanisms (*5*). In the case of levetiracetam, an earlier study reported a patient with DIP due to levetiracetam administered for Huntington's disease (*18*); however, this patient had taken olanzapine and paroxetine, so the true contribution of levetiracetam to the development of parkinsonism in the current data remains unclear.

The maximum length of the disease-free survival of patients with DIP on dopamine antagonists of more than 2-10 years suggests that it may be longer in range. In other words, when a patient who has used sulpiride for more than 10 years exhibits acute-onset parkinsonism, the possibility of sulpiride-induced parkinsonism cannot be ruled out until confirmation by discontinuing sulpiride. Long-term use of dopamine antagonists will eventually lead to slowly progressing dopaminergic degeneration in patients with prodromal PD (*5,14*).

The current study has several limitations due to the nature of its use of a self-reporting database (*6*); it includes several types of bias that cannot be eliminated in this type of study. First, there may be reporting bias: dopamine-antagonist drugs are known to cause DIP, whereas other drugs, such as antiepileptic drugs or CCBs, may not always cause DIP. Such a discrepancy may prejudice a clinician to believe that non-dopamine antagonists are less likely to be the cause of parkinsonism, so those reactions may be less likely to be reported to JADER. In addition, due to the lack of denominators, the incidence of DIP for each drug cannot be discussed and potentially causative drugs cannot be differentiated from other types of drugs. Moreover, other types of medications or concurrent/past medical history that are potentially related to the development/worsening of DIP were not considered, nor was the concurrent use of potentially causative drugs. Disease-free survival is sometimes not accurate, and the total dose of drugs was not considered in this analysis.

In conclusion, the current results demonstrated that disease-free survival might substantially differ depending on the types of drugs causing DIP. This is informative for clinicians when diagnosing patients with parkinsonism.

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Brief Report

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Bacteriophage therapy for empyema caused by carbapenem-resistant *Pseudomonas aeruginosa*

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SUMMARY *Pseudomonas aeruginosa* is a frequent causative agent of post-pneumonectomy empyema-associated broncho-pleural fistula (BPF) and it has a high mortality rate. In recent years, the therapeutic potential of bacteriophage therapy has recognized anew as antimicrobial resistance increases globally. Studies are increasingly reporting the efficacy and safety of bacteriophage therapy for the treatment of multidrug-resistant bacterial infections. However, the clinical efficacy of bacteriophage therapy in empyema has seldom been studied. The current study reports the authors' experience with bacteriophage therapy for a 68-year-old Chinese man who suffered BPF-associated empyema and pneumonia caused by carbapenem-resistant *P. aeruginosa*. A personalized lytic pathogen-specific two-phage preparation was administered to the patient continuously for 24 days in combination with conventional antibiotics. The treatment was well-tolerated, resulting in clearance of the pathogen and improvement of the clinical outcome. This experience shows that a combined conventional antibiotic treatment with bacteriophage therapy may be effective at alleviating a multidrug-resistant bacterial infection in BPF-associated empyema.

Keywords bacteriophage therapy, empyema, carbapenem-resistant *Pseudomonas aeruginosa*, pneumonia, broncho-pleural fistula

1. Introduction

Post-pneumonectomy empyema is the most severe complication of pneumonectomy (*1*). It is often associated with broncho-pleural fistula (BPF) (*2*). Stern *et al*. reported that the mortality rate of early (within 2 weeks of surgery) BPF-associated empyema was 19% and that the 1-year survival rate of early BPF-associated empyema was 47% (*1*). The organism most commonly isolated from specimens is *Pseudomonas aeruginosa* (*3*). Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is one of the critical priority pathogens on the WHO's list. Evaluating the efficacy of new antibiotics is difficult and expensive, and especially when targeting multidrug-resistant Gram-negative bacteria (*4*). Thus, new methods for the treatment of CRPA need to be explored.

In recent years, bacteriophage therapy has been used on hard-to-treat bacterial infections, and there are several reported examples of the successful treatment of infections caused by CRPA (*5,6*). However, the clinical efficacy of bacteriophage therapy in empyema has seldom been studied. Reported here is the current authors' experience with bacteriophage therapy in a case of BPF-associated empyema and pneumonia caused by CRPA.

2. Methods

2.1. Bacteriophage preparation

Two lytic phages, PA3 and PA18, were chosen for bacteriophage therapy. The plaques of PA3 and PA18 on a lawn of *P. aeruginosa* are shown in Figure 1. The phage preparation was purified in a cesium chloride density gradient and then dialyzed using a Spectra/Por 6 membrane (MWCO 25 kDa, Sanoon Biotech, Shanghai, China) in SM Buffer (without Tris-HCl) to remove cesium chloride. Phages were then sterilized through 0.22-μm filters. Phages were titrated and evaluated

for endotoxins with an End-point Chromogenic Endotoxin Test Kit (Bioendo, Xiamen, China). The phage preparation was subsequently stored at 4°C until required.

2.2. Data collection

Clinical laboratory data including the white blood count (WBC), percentage of neutrophils (N%), sedimentation rate (ESR), procalcitonin (PCT) level, C-reactive protein (CRP) level, and liver and renal function were collected. Results of cultures of sputum, pleural effusion (PE), and bronchoalveolar lavage fluid (BALF) were also examined.

2.3. Patient surgical intervention

The patient's lung had been destroyed after tuberculosis and repeated hemoptysis for 2 years. A right upper lobe resection was performed *via* video-assisted thoracoscopic lobectomy, and the pleura was decorticated on December 10, 2021. After surgery, he suffered from empyema with BPF, which was treated with continuous negative pressure suction. A membrane-covered stent was inserted into the trunk bronchial stump *via* a bronchoscope on January 4, 2022. Due to continuous air leakage, the stent and negative pressure suction device were removed and an open-window thoracostomy was performed for the management of empyema on January 18, 2022.

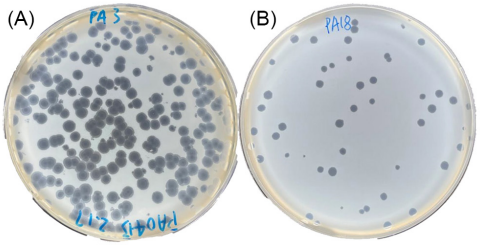

Figure 1. Plaques of PA3 (A) and PA18 (B) on a lawn of P. aeruginosa.

3. Results and Discussion

3.1. Clinical history before phage therapy

A 68-year-old Chinese male was admitted due to an intermittent cough, sputum for 7 years, and hemoptysis for 2 years. He was diagnosed with pulmonary tuberculosis in 2014 and treated with an anti-tuberculosis drug for 1 year. In 2016, he had a second episode of pulmonary tuberculosis and received anti-tuberculosis treatment for 6 months. He had recurrent hemoptysis starting in 2020 and was treated again with the anti-tuberculosis drug for 3 months. After admission, he was diagnosed with a destroyed right lung, bronchiectasis with a *P. aeruginosa* infection, and obsolete pulmonary tuberculosis. After the right upper lobectomy, he developed empyema with BPF and pneumonia. *P. aeruginosa* was isolated from cultures of sputum, BALF, PE, and lung tissues obtained during surgery. He was treated with a variety of antibiotics including amikacin, azithromycin, imipenem, and ceftazidime-avibactam (Figure 2). A PE culture was positive for CRPA on January 12, 2022. After obtaining consent from the Ethics Committee of the Third People's Hospital of Shenzhen (ethics approval no. 2021-068) and the patient's family for experimental treatment, phage therapy was initiated.

3.2. Bacteriophage therapy and clinical outcome

The bacteriophage was nebulized twice daily and injected intrapleurally once daily between January 14 and 25, 2022. Following the intrapleural injection, negative pressure drainage was stopped for 4 hours. Amikacin, ceftazidime-avibactam, and fosfomycin were concomitantly administered intravenously. Since *P. aeruginosa* was still present in PE on January 19 (reported on January 22), the dose of the phage was increased on January 25 (11 days after phage therapy). The phage that was intrapleurally injected daily remained in the right pleural space until the next day. The bacteriophage was nebulized three times on January 25 and 26 and then nebulized twice daily.

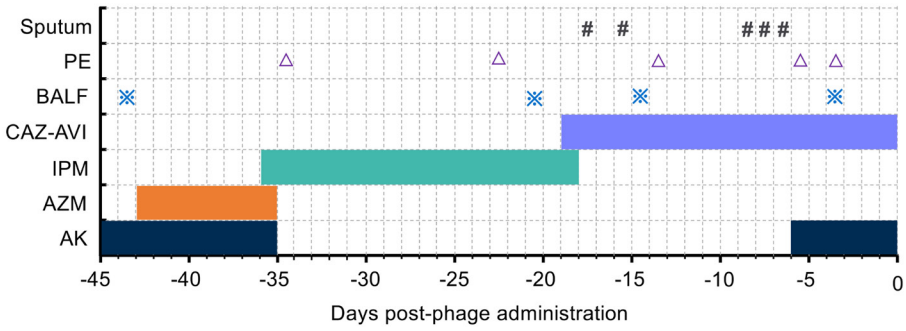

Figure 2. Bacterial culture and antibiotics administered before bacteriophage therapy. CRPA-positive cultures from sputum (#), PE (Δ) and BALF (※). PE, pleural effusion; BALF, bronchoalveolar lavage fluid; CAZ-AVI, ceftazidime-avibactam; IPM, imipenem; AZM, azithromycin; AK, amikacin.

Table 1. Details of the bacteriophage administration

Bacteriophage cocktail	Component bacteriophages	Titer (PFU/mL)	Endotoxin concentration (EU/mL)	Route of administration and frequency
1	PA3	1.25×10^{10}	190	0.4 mL of phage was added to 4.6 mL normal saline nebulized twice or three times daily or intrapleural injected once daily
	PA18	1.25×10^{10}		
2	PA3	3.0×10^{10}	2,200	
	PA18	1.5×10^{11}		

EU, endotoxin units; PFU, plaque forming units.

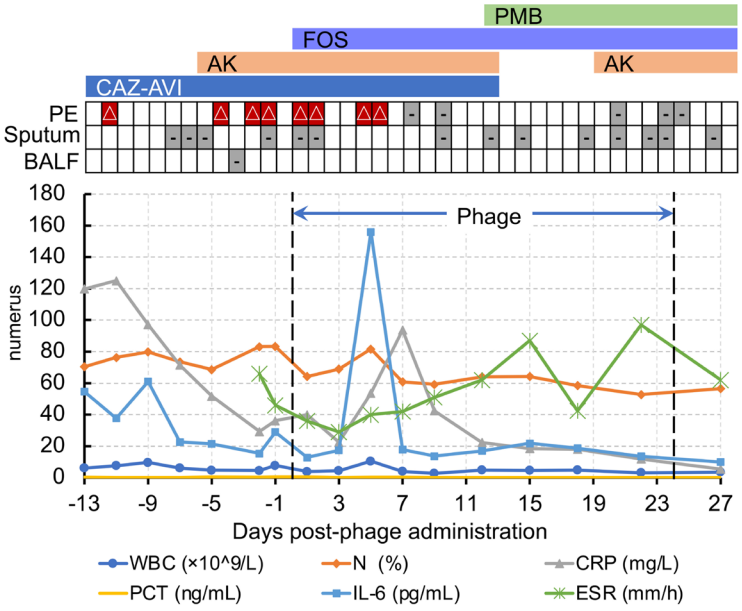

Figure 3. Patient clinical data during phage therapy. (A). Graph of bacterial cultures, inflammatory markers, and the duration of antibiotic and bacteriophage administration. CRPA-positive cultures from PE (Δ), CRPA-negative cultures from PE and sputum (-).

Fosfomycin and polymyxin were also administered then. The details of phage administration are shown in Table 1. All antibiotics were stopped 28 days after phage therapy.

P. aeruginosa was isolated from PE samples on day 0, 1, 4, and 5 after phage therapy. Carbapenem-sensitive *P. aeruginosa* was detected on February 27, 2022, from day 7 of phage therapy to discharge, but cultures of PE did not yield any CRPA (Figure 3 A). Carbapenem-sensitive *P. aeruginosa* was considered to be a colonizer since the patient did not have any symptoms and the volume of PE did not increase.

Inflammatory markers including WBC, N%, PCT, ESR, CRP, and IL-6 tended to gradually decrease during the period of bacteriophage therapy, although a peak in IL-6 was observed on day 5 after therapy and a peak in CRP was observed on day 7. Changes in the levels of IL-6 and CRP were presumably caused by the open-window thoracostomy. In addition, there were no serious adverse reactions to the therapy in terms of the patient's liver and renal function except for a slight increase in liver function that was observed on day 18 after phage therapy, when polymyxin B was administered. Liver function quickly returned to normal after polymyxin was stopped (Figures 3 A and 3 B). Moreover, the volume of PE decreased and the consolidations evident on pre-treatment chest X-rays and CT scans gradually improved (Figures 3 C and 3 D). The patient did not have a cough, sputum, or shortness of breath when he was discharged from the hospital on March 4, 2022.

Empyema has been described as a possible sanctuary for drug-resistant bacteria since antibiotics have been proven to reach the site of infection at subtherapeutic concentrations, thus increasing the risk of treatment failure (*7*). The delivery of phages to the desired site remains a major challenge for bacteriophage therapy. In the current case, the phage preparation was administered locally *via* an intrapleural injection to eradicate empyema. Due to safety concerns, negative pressure drainage was stopped only for 4 hours initially following the intrapleural injection. However, PE cultures were still positive for CRPA after 5 days of treatment (Figure 3A). The phages did not seem to have reached the site of injection. After open-window thoracostomy, the phages that were injected intrapleurally remained in the right pleural space for a longer period. No CRPA was detected in PE cultures from then on, and the patient was discharged with no signs of infection.

Above all, bacteriophage therapy was well-tolerated

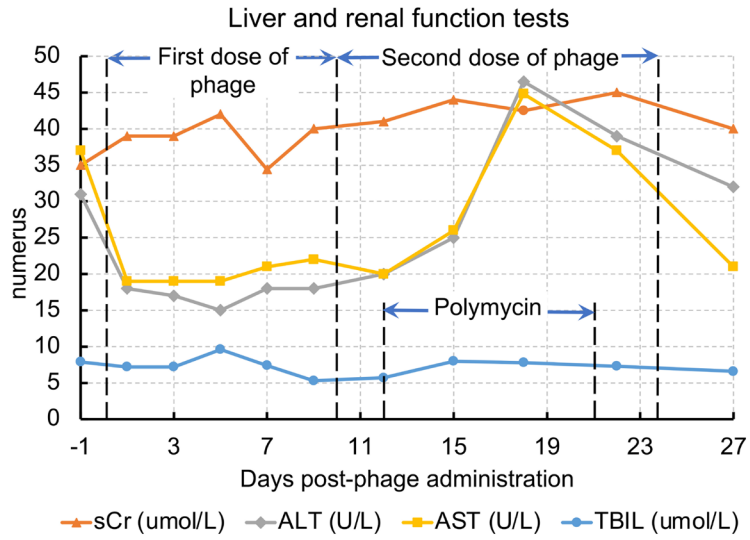

Figure 3. Patient clinical data during phage therapy. (B). Graph of liver and renal function test results over time during phage therapy.

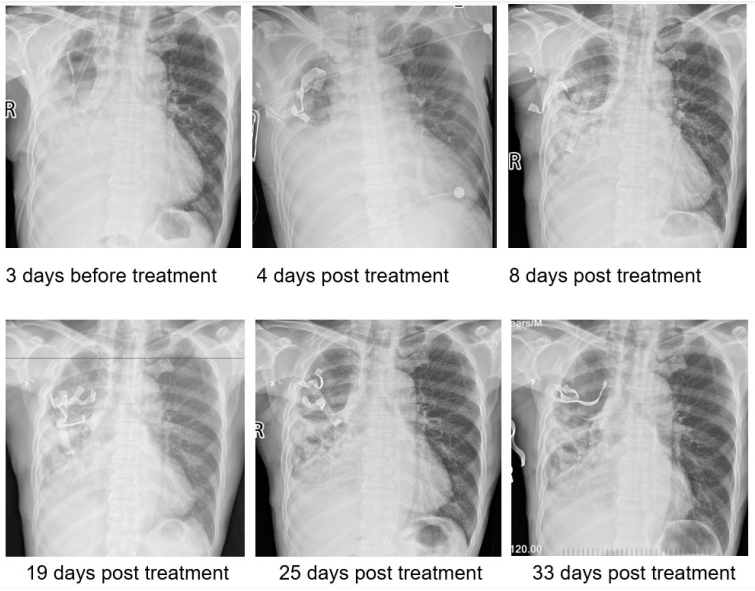

Figure 3. Patient clinical data during phage therapy. (C). The patient's chest X-rays 3 days before phage therapy and on day 4, 8, 19, 25, and 33 after phage therapy.

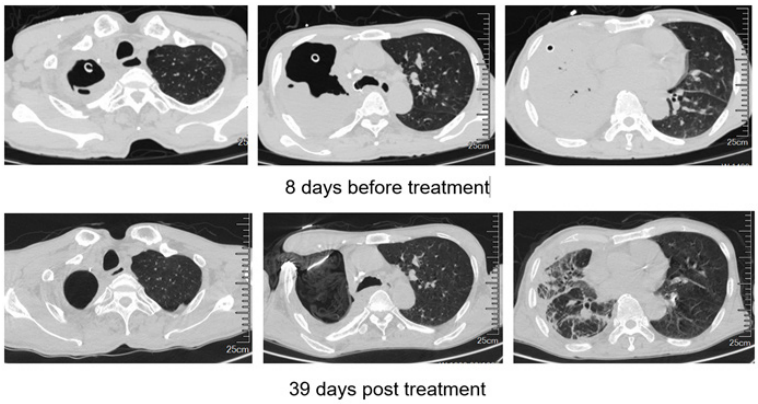

Figure 3. Patient clinical data during phage therapy. (D). The patient's chest CT scans 8 days before phage therapy and on day 39 after phage therapy.

in the current patient, with no obvious phage-associated adverse events. Adverse reactions associated with the host's defense mechanisms against a *P. aeruginosa* phage require further evaluation (*8*). The current experience shows that conventional antibiotic treatment in combination with bacteriophage therapy may be effective at alleviating a multi-drug resistant bacterial infection. However, measures such as local drug delivery systems, surgical interventions, and repeated courses of a phage are vital to clinical success in cases of surgical site infections. In a critical era of increasing antimicrobial resistance, bacteriophage therapy warrants further evaluation in well-designed clinical trials for larger-scale use.

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Communication

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An innovative two-wing model for balancing the demands of inpatients with COVID-19 and general medical service in a designated hospital for COVID-19 in Shenzhen, China

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SUMMARY Since COVID-19 was first reported in 2019, the pandemic has posed a great threat to human health. Due to its multiple transmission pathways and virus mutation, this epidemic may be protracted further, and it has already placed a heavy burden on healthcare systems. A strategy needs to be devised to address both needs for COVID-19 treatment and demands for general medical service. A two-wing model of hospital operation, which provides a safe treatment environment for patients, an On duty/On Standby work approach for medical staff, and a reliable surveillance system for hospital operation, is an effective management template to help achieve a balance between multiple demands for medical service in this new era of a long-term war against COVID-19.

Keywords SARS-CoV-2, model of hospital operation, healthcare personnel

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), which has thus far infected over 430 million people globally (*1*). Droplets, aerosols, physical contact, and the digestive tract are all possible transmission pathways (*2,3*). Due to its multiple transmission pathways and virus mutation, this epidemic could be further protracted, and it has already placed a heavy burden on healthcare systems (*4*). A strategy needs to be devised to address both needs for COVID-19 treatment and demands for general medical service. As the designated hospital for COVID-19 in Shenzhen, a city with over 12 million residents, this facility has developed an innovative two-wing model of operation (Figure 1). This mode involves a safe treatment environment for patients, an On Duty/On standby work approach for medical staff, and a reliable surveillance system. To the extent known, this is the first hospital to adopt such a model to balance and address demands for general medical care and COVID-19 treatment in China.

2. Two wings of the hospital

In the early stages of the COVID-19 pandemic in January 2020, there were over 18 admissions per day on average to this hospital. Given the potential for nosocomial infection among patients, most other patients were transferred to other hospitals. Afterwards, an isolation wing located next to the original wing was officially opened in June 2020, with negative pressure wards for patients. Patients with COVID-19 were admitted to the isolation wing, whereas patients with other conditions were admitted to the original wing. In line with this two-wing approach, 1,739 patients with COVID-19 were admitted to the isolation wing as of February 28, 2022, while medical personnel in the original wing cared for an average of 1,836 outpatients and 832 inpatients per day. Evaluation of the quality of hospital administration is a complex task that involves numerous variables, the most essential and sensitive of which are patient satisfaction and treatment outcomes (*5*). Patient satisfaction with this hospital's care was an average of 92% and the rate of successful treatment was an average of 86% while the two-wing model has been operation. There were no nosocomial infections in either wing and no deaths among inpatients with COVID-19.

(A)

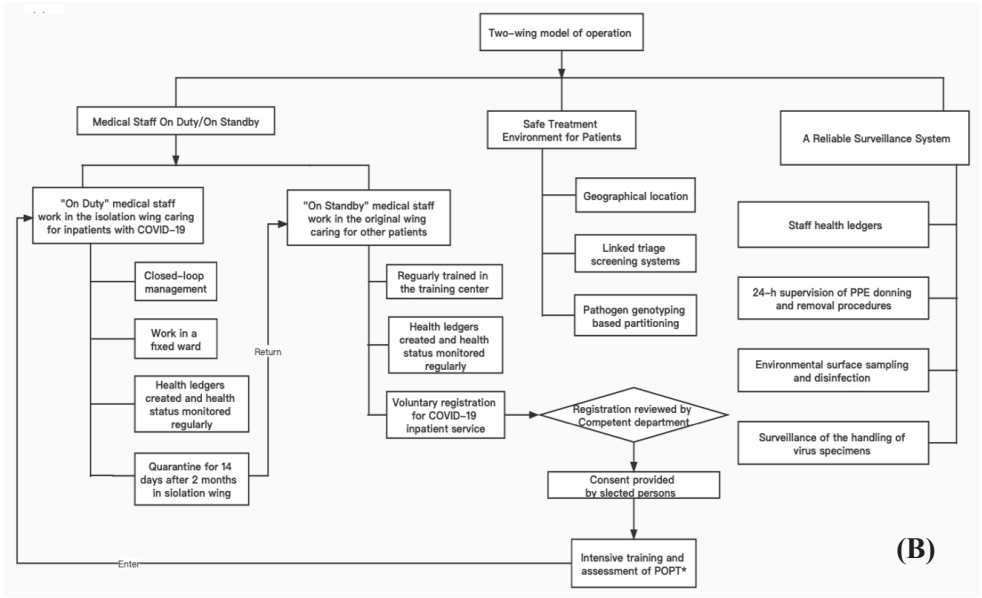

Figure 1. (A), Layout of the two wings. (B), Two-wing model of operation. * POPT: Personal Occupational Protection Technology.

3. Three characteristics of the two-wing model of operation

3.1. Safe treatment environment for patients

3.1.1. Geographical location

The two wings are adjacent, and there is a small hillside between them that acts as a natural barrier (Figure 1). The isolation wing is located downwind of the original wing, and air flows from the original wing to the isolation wing, which satisfies the layout requirements for an site to treat airborne diseases (*6*). Moreover, negative pressure in the isolation wards allows for the disinfection of contaminated air in patient wards before discharge. Both features ensure the biosecurity of air in the surrounding area.

3.1.2. A triage screening system

During the COVID-19 pandemic, patients with relevant symptoms of COVID-19 must undergo screening to rule out COVID-19 before completing subsequent medical treatment. Fever clinics 1 and 2 were established in the isolation wing and original wing, respectively. Patients with relevant symptoms are screened in fever clinic 2, whereas those with an epidemiological history or suspected cases are screened in fever clinic 1, where a dedicated ward was set up for patients suspected of having COVID-19 to wait for their screening results in a single room. A previous study by the current authors (*7*) indicated that the rate at which inpatients with COVID-19 were detected by fever clinic 1 was significantly higher than that the rate at which inpatients were detected by fever clinic 2, indicating that the linked triage screening system (Figure 2) can lower the risk of cross-infection among out-patients.

3.1.3. Pathogen genotyping-based separation of COVID patients and staff

Given the differing level of pathogenicity among SARS-CoV-2 variants (*8,9*), patients were assigned to separate wards based on viral genotypes to avoid cross-infection

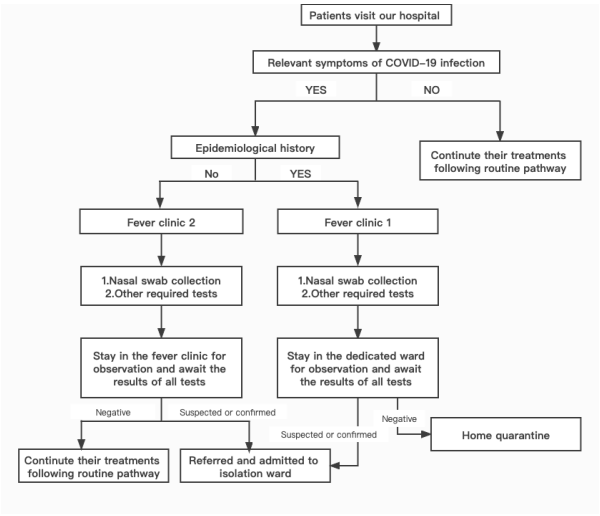

Figure 2. The operation of a triage screening system.

among inpatients. A closed-loop pattern for the handling of virus specimens was also implemented. An electronic monitoring system is used to constantly monitor the status of specimens, including the state of detection, the individual who delivered the specimen, and inspectors. Medical personnel and inspectors are restricted from working in multiple wards and laboratories dealing with different genotypes. Their accommodations are also separated.

3.2. Medical personnel who are "On Duty/On Standby"

Along with vaccination campaigns and other measures, China has made tremendous success in controlling the epidemic. Healthcare personnel are extremely valuable and crucial in addressing the COVID-19 crisis since they are the key to quality healthcare (*10,11*). The two-wing model involves an "On Duty/On Standby" approach to work by personnel based on the severity of the epidemic, which allow medical facilities make the best use of human resources and maintain their mental health.

While "On Standby": In the original wing, there are 37 units dedicated to the treatment of conditions other than COVID-19. Staff who work in the original wing are considered to be "On Standby." While on standby, they provide care to patients with conditions other than COVID-19 and they also receive skill training. A point worth noting is that a training center for infectious disease scenarios, the first of its kind in China, was built; this immersive teaching approach enhances the skills of medical personnel without requiring them to enter infectious disease wards. With the support of this training center, medical personnel are always "On Standby" to care for patients with COVID-19.

While "On Duty": Staff who work in the isolation wing are "On Duty". Staff come "On Duty" when an outbreak of COVID-19 occurs or "On Duty" workers rotate in and out. Medical staff can voluntarily sign up to work in the isolation wing and are selected by a competent department depending on their health status, experience, skill in treating infectious diseases, etc. Selected individuals will rotate into isolation wards, with each shift lasting two months. Closed-loop management of isolation wing personnel has been implemented, including designated accommodations while working and quarantine in a designated hotel for 14 days after they finish work in the isolation wards. Regular rotation can substantially safeguard the mental health of medical staff and reduce the adverse impact that isolation might have.

3.3. A reliable surveillance system

3.3.1. A system to surveil the health status of personnel

Health ledgers were created for medical staff, general staff, patient escorts, and other visitors to the hospital to monitor their health status and identify high-risk individuals or individuals suspected of being infected at the earliest stage possible. The ledger contains health information, including temperature, relevant COVID-19 symptoms, COVID-19 vaccination status, and the antibody titer. In addition, medical staff are tested for COVID-19 on a regular basis, with the frequency varying depending on their working conditions. For staff working in the isolation wing, testing is conducted once every one or two days, while for those in the original wing, it is conducted once every week or varied depending on the status of the epidemic.

3.3.2. 24-hour supervision of personal protective equipment donning and removal

Personal protective equipment (PPE) is essential for avoiding occupational exposure, and especially when working in a contagious environment (*12*). However, one study reported that occupational exposure was sometimes caused by improper wearing and removal of PPE resulting in contamination of the hands or mucous membrane (*13*). In the designated hospital for COVID-19, a monitoring system was implemented and an intercom was used to supervise PPE wear 24 hours a day in isolation wards and to identify high-risk procedures and individuals when donning and removing PPE based on collected data (*14*). These results helped to revise and prioritize training plans, resulting in a more efficient training system.

3.3.3. Environmental surface sampling and disinfection

SARS-CoV-2 has been proven to spread via many routes (*2,3*). The current authors previously found that there was no correlation between environmental factors and symptoms in patients with COVID-19 (*15*). Disinfection of contaminated surfaces is as critical as disinfection of

other transmission pathways. High-risk contaminated surfaces, including door handles, patient beds, and the ward floor, were regularly sampled in both the isolation and original wings to detect the virus. The frequency of sampling in the two wings varied depended on the risk level in different areas and ranged from twice a week to once a month. The disinfection of environmental surfaces varied depending on the area.

4. Conclusion

The adoption of a two-wing model in a designated hospital for COVID-19 has provided an effective management template for a normalization response to pandemic control, and especially in terms of preventing nosocomial transmission and effective utilization of medical resources. This approach can help to achieve a balance between COVID-19 management and general demands for medical service in this new era of a long-term war against COVID-19.

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Commentary

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Current status of and challenges posed by autism spectrum disorders in China: Prevalence, legal issues, and public awareness

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SUMMARY Over the past 30 years or so, the body of research on autism spectrum disorders (ASD) in China has grown steadily. With the tireless efforts of government agencies and private organizations, the legitimate rights and interests of children with ASD have been initially guaranteed through a series of education and rehabilitation reforms, yet there are still many challenges to overcome. Many quality studies on the prevalence of ASD have been conducted in recent years, but China has lacked official census data until now. Moreover, there is a general lack of awareness of ASD even among the groups that directly interact with individuals with ASD, namely parents/caregivers, teachers, and doctors. Despite that fact, ASD should be brought to the attention of professionals and policymakers so that they can take appropriate measures, which include *i*) early comprehensive screening and diagnosis of ASD, *ii*) improvement of the corresponding policies and regulatory system, and *iii*) promotion of public awareness of ASD.

Keywords autism spectrum disorders, prevalence, legal issues, public awareness

1. Introduction

Autistic spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social interaction and communication, as well as restricted, repetitive, and stereotyped patterns of behaviors, interests, and activities (*1*). Although the disorder is closely related to genetic factors, there is no form of prenatal screening for ASD like there is for Down syndrome (*2*). Therefore, perinatal care for pregnant women, and especially women of advanced maternal age, is crucial to reducing the risk of ASD onset (*3*). Globally, 0.76% of people worldwide suffer from the disorder (*4*), resulting in a heavy economic burden for both families and society as a whole. Research on ASD was initiated relatively late in China, so the first case in a child was not diagnosed and reported until 1982 (*5*). Since more attention is being devoted to autistic children in China, research on ASD has tended to increase in recent years. Statistics indicate that the number of articles published by Chinese scholars on the topic of "autism" increased from only 9 in 1993 to 5,674 in 2021. The current review summarizes the recent trends in prevalence, national policy, and public knowledge of ASD over the past few decades, and it offers recommendations to professionals and policymakers on how to better help individuals with ASD.

2. Prevalence of ASD in China

So far, there are no official statistics on the prevalence of ASD in China (*6*), but a meta-analysis summarized the prevalence of ASD in 26 studies published from 2000 to 2016, yielding an estimated prevalence of 0.3% on the Chinese mainland (*6*). Due to the use of non-standard methodologies (*7*), the prevalence reported in China is regrettably believed to be underestimated (*8,9*). A point worth noting, however, is that recent studies have identified and sought to remedy these flaws, leading to more accurate figures. Currently, the largest epidemiological study conducted in eight cities estimated the prevalence of ASD nationwide to be 0.70% (*8*), which is closer to global estimates of its prevalence (*4*). Details on representative epidemiological studies on ASD in China over the past few years are shown in Table 1. However, the vast

Table 1. Summary of representative epidemiological studies published since 2019 in China

Year	Region	Prevalence /1000 (95% CI)	Screening tools	Diagnostic criteria	Age (years)	Sample size	*Ref.*
2019	Jilin	10.8 (8.7, 13.5)	CAST	ADOS; ADI-R; DSM-IV-TR; DSM-5	6 to 10	6,149	(*9*)
	Shenzhen	4.2 (2.0, 8.9)				20,802	
	Jiamusi	1.9 (1.0, 3.8)				15,663	
2020	Nationwide	7.0 (6.4, 7.4)	MC-ASRS; WISC-C; MINI-kid	ADOS; ADI-R; DSM-5	6 to 12	125,806	(*8*)
2021	Wuhu	4.11 (2.8, 4.9)*	CARS	DSM-5	2 to 6	12,657	(*27*)
2021	Inner Mongolia	2.66 (1.6, 3.5)*	CABS; ABC	DSM-5	3 to 14	15,817	(*28*)

*Prevalence estimates and/or 95% CIs calculated from information reported in the original papers. Nationwide: Shanghai, Guangzhou, Changsha, Harbin, Beijing, Chongqing, Chengdu, Wenzhou. ABC, Autism Behavior Checklist; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Scale; CABS, Clancy Autism Behavior Scale; CARS, Childhood Autism Rating Scale; CAST, Children Autism Spectrum Test; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; MC-ASRS, modified Chinese version of the Autism Spectrum Rating Scale; MINI-kid, Chinese Mini International Neuropsychiatric Interview for Children and Adolescents-Parent Version; WISC-C, Wechsler Intelligence Scale for Children in Chinese.

majority of the population with ASD living in remote or backward areas still tends not to be diagnosed due to the shortage of medical personnel, public ignorance, and parental concealment (*6*), implying a higher level of prevalence. The speculation is that the number of patients with ASD exceeds 10 million in China, more than 2 million of whom are children (*10*). The increasing prevalence of ASD has attracted the attention of the government.

3. Laws, regulations, and policies on ASD in China

China enacted a slew of legislation since the mid-1980s with the goal of helping the disabled, and especially through special education. In 1986, the government adopted the Compulsory Education Law, providing disabled individuals with access to public education, and then "Suiban Jiudu", literally learning in regular classrooms, became the dominant form of special education in 1988 as a result of the influence of foreign "inclusive education" (*11*). The Law on the Protection of the Disabled promulgated in 1990 further emphasized the necessity of protecting the right to education of the handicapped. With the help of the 1994 Regulations on the Education for the Disabled, more detailed regulations and distinctions have been made in terms of methods of instruction and curricula. Eventually, the aforementioned laws and regulations promoted comprehensive universal basic education for all children, including those with disabilities (*11*).

Regrettably, early legislation only described principles and it provided very general and spotty protections for the mentally disabled. There is no specific policy guaranteeing an education to children with ASD, who are often turned away from government-run public schools, including special education schools (*12*). Nevertheless, once autism was included as a mental disability, the state specifically proposed education for children with ASD for the first time in 2009, reflecting the country's particular attention to their compulsory education (*12*). At present, special education has entered a new phase. Relevant departments additionally launched two phases of a plan to promote special education, ultimately resulting in an enrollment rate among children with disabilities of more than 95% and an enrollment in special education (including children with ASD) of 149,046 by the end of 2020 (*13*). To ensure the development of rehabilitation in conjunction with education, a series of guidelines and rehabilitation policies were successively promulgated, gradually creating a national system of rehabilitation assistance for disabled children (*14*). Figure 1 shows a timeline of major events and milestones in the development of China's laws, regulations, and policies on ASD since the 1980s.

4. The public's knowledge, attitudes, and perceptions towards ASD in China

There has been speculation that a lack of public awareness of ASD might contribute to an insufficient understanding of the disorder in China (*7,9,15*). Described below is the current status of ASD awareness among three main groups of Chinese: parents/caregivers, educators, and medical personnel.

4.1. Parents/caregivers

In general, Chinese parents of children with ASD lack basic knowledge about the condition (*16*). They often suffer from great psychological pressure and social discrimination because of negative media portrayals and social stigmatization (*6,16-19*), resulting in the reduced likelihood of seeking diagnosis, intervention, and support (*16,19*). Worse still, these parents usually prevent their children from interacting with outsiders to hide what they consider to be the shameful truth (*16*). Moreover, approximately 40% of families of children with ASD face heavy indebtedness after incurring rehabilitation costs are (*6*), and almost 60% of families experience interpersonal conflict and job loss because of parenting

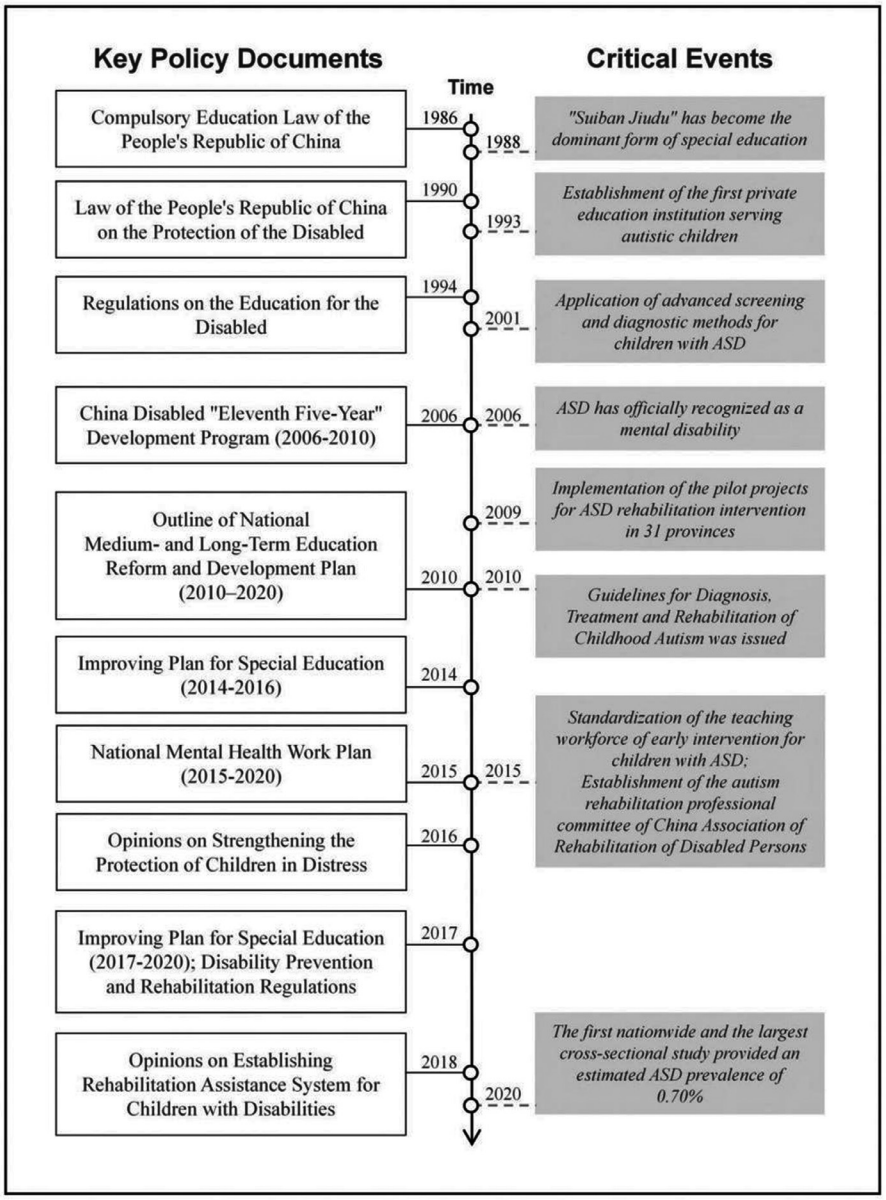

Figure 1. Brief timeline of China's ASD strategy since 1986. Key policy documents are mainly related to education and rehabilitation. Major national initiatives or landmarks are cited as critical events.

demands (*20*). Increasing expenses for education and rehabilitation have made families more vulnerable, affecting their well-being in a substantial way (*21*), which explains why most parents feel hopeless and pessimistic about their children's future.

4.2. Educators

Teachers with knowledge of ASD have been in short supply in China's education system for a long time (*6,15*). A recent study indicated that the majority of teachers were not familiar with the general situation of and interventions to deal with ASD, reflecting a lack of training in special education (*15*). Although experience working with disabled children might compensate this deficit, paradoxically the reason for children with ASD are most often denied school admission is the lack of experienced teachers to work with them (*22*). Notably, some teachers are reluctant to accept autistic children in their classes, but most teachers are eager to teach children with disabilities and would like to do more to help students with disabilities, including ASD (*15*). Accordingly, some scholars have proposed the concept of pre-service and post-service teacher training, which may lead to a more optimistic future for children with ASD in China (*23*).

4.3. Medical personnel

An absolute lack of ASD-related knowledge among medical personnel prevailed on the Chinese mainland. Doctors at community clinics and local hospitals have little education or professional training in child psychiatry (*7*), so most children with ASD are diagnosed only at tertiary hospitals in large cities (*24*). On the one hand, child healthcare workers are relatively young, with comparatively little work experience (*25*); on the other hand, they have relatively low levels of education

(*25*), and even highly educated or pediatricians also have minimal training in child and adolescent psychiatry (*7*). Thus, the fact that they know little or even less than parents of children about ASD is not surprising. More alarmingly, there is still an acute shortage of pediatricians and pediatric psychiatrists in China (*7,26*). They are concentrated in relatively developed areas such as Beijing, Shanghai, and Guangzhou, resulting in an uneven distribution and vast disparity in levels of care (*26*).

5. Suggestions and outlook for the future

Despite some progress and achievements, there are still some deficiencies and urgent issues that need to be addressed: *i*) Expanding the coverage of screening for children with ASD. The prevalence of ASD in China needs to be monitored continuously at the national level to obtain accurate data about its incidence to understand the course of the disorder; *ii*) Improving assistance and treatment for children with ASD; and *iii*) Raising public awareness of ASD. Research on ASD should be publicized in a comprehensive manner to garner society's attention and awareness, and an understanding of ASD should be promoted among key groups to ensure a good environment so that children with ASD can to integrate into society.

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Commentary

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Autism spectrum disorder: Status of primary care in China

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SUMMARY Primary care serves as the cornerstone to ensure positive health outcomes for diseases. Autism spectrum disorder (ASD) has attracted more attention as a lifelong neurodevelopmental disorder with a prevalence that is increasing yearly. Although the demand for primary care for ASD is rapidly expanding, there are many challenges that need to be faced. Here, the current status of primary care for ASD in China is described. *i*) Identification of and care for ASD includes pre-diagnosis, diagnosis and evaluation, and treatment; the complexity of the disease and the lack of public understanding increase delays in diagnosis and treatment. *ii*) Most instruments, which are indispensable for diagnosing and evaluating ASD, are of foreign origin. *iii*) Treatments for ASD are based on mainstream Western interventions with complementary approaches. *iv*) The scale of rehabilitation and educational institutions has gradually grown and their expertise has gradually increased but rehabilitation costs are relatively high.

Keywords autism spectrum disorder, primary care, diagnosis, treatment

1. Introduction

Autism spectrum disorder (ASD), characterized by difficult social interaction and communication, narrow interests, and stereotyped repetitive behaviors, is a neurodevelopmental disorder that originates in early childhood (*1,2*). A nationwide multi-center population study found that the prevalence of ASD in children ages 6-12 was about 0.70% on the Chinese mainland (*3*), which was similar to a global prevalence of 0.76% (*4*). ASD is a lifelong disorder with a prevalence that is increasing yearly, and patients require long-term care and support in areas such as healthcare, education, and community services, posing a heavy economic burden to their families and society (*5,6*). In addition, the long-term stigma suffered by family members negatively affects their physical and mental health (*7*).

Primary care broadly refers to a type of public health and is narrowly a healthcare approach that provides medical care to the public (*8*). An important guarantee is that people with ASD can obtain long-term medical support, which not only increases access to medical care but also reduces the negative impact of economic concerns on health (*9*). Here, the current status of primary care for ASD in China is described in terms of approaches to and methods of diagnosing and treating ASD and rehabilitation and educational institutions.

2. Current status of ASD diagnosis and treatment in China

Generally, most patients need to undergo three complex processes: pre-diagnosis, diagnosis and evaluation, and treatment (Figure 1). Unlike diseases such as Down syndrome that can be diagnosed early by prenatal and postpartum chromosomal tests (*10*), ASD can only be diagnosed via an assessment of abnormal behaviors, which may be not well understood by many Chinese parents or doctors in primary hospitals (*11*). In addition, the number of doctors cannot meet the ever-increasing demand for care (*12*), and psychiatrists and psychologists specializing in diagnosing and treating children with ASD are especially in short supply, resulting in a limited capacity for primary care in local hospitals, private practices, and community centers (*11*). Consequently, the complexity of ASD and the lack of understanding of the disorder results in an average delay of one year from identification of symptoms to proper treatment (*13-15*). Although an expert consensus on early screening and intervention for Chinese children with ASD was reached

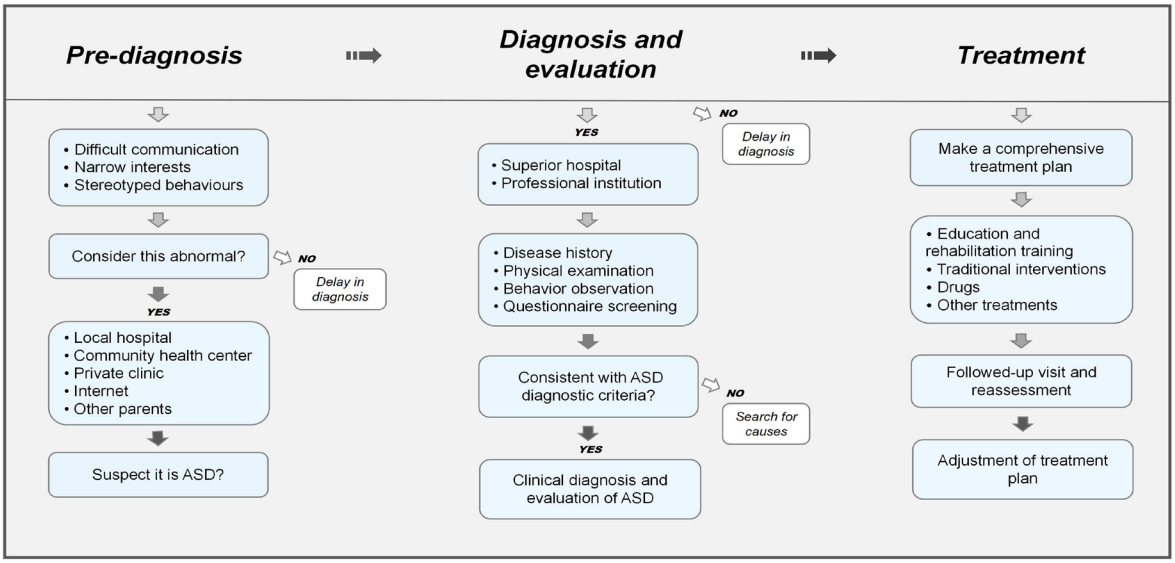

Figure 1. Flowchart for primary care for ASD in China. Identification of and care for Chinese patients with ASD can be summarized into three processes: Pre-diagnosis, diagnosis and evaluation, and treatment. ASD, autism spectrum disorder.

Table 1. ASD screening and diagnostic tools commonly used in China

Category	Tool name	Applicable age groups	Main purpose	Features
Screening tools	CHCIA, M-CHAT, SORF ASSS, CABS ABC	Infant Child Infant to adult	Screening or initial diagnosis of patients with ASD	• Relatively easy to use; • Filled in by the caregiver; • Positive results require further testing.
Diagnostic and assessment tools	CARS C-PEP-3 ADI-R, ADOS, SRS-2	Child Infant, child Infant to adult	Diagnosis and differential diagnosis or assessment of ASD	• Used by professionals; • Time-consuming; • Larger population covered.

Data source: Reference (*19*). Infant, < 4 years of age; Child, 5-13 years of age; Infant to adult, including infants, children, adolescents, and adults. ABC, Autism Behavior Checklist; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; ASSS, Asperger's Syndrome Screening Scale; CABS, Clancy Autism Behavior Scale; CARS, Childhood Autism Rating Scale; CHCIA, Checklist for China's Infants With Autism; C-PEP-3, Third Edition of the Revised Chinese Version of the Psycho-Educational Profile for Children with ASD & Developmental Disabilities; M-CHAT, Modified Checklist for Autism in Toddlers; SORF, Systematic Observation of Red Flags; SRS-2, Social Responsiveness Scale, Second Edition.

in 2017 (*16*), early ASD screening has unfortunately not been included in the public health projects of community health service centers, and only a few large cities have implemented such a program through cooperative projects (*11*).

3. Screening and diagnosis of ASD in China

Early diagnosis and treatment are more conducive to alleviating the symptoms of patients with ASD and integrating them into society as much as possible (*16,17*). Methods of diagnosing ASD via imaging studies or blood biochemistry are still in the preclinical study phase (*18*). Presently, the diagnosis of ASD by domestic medical personnel is mainly based on the diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed, which is dependent on the caregiver's description of unusual behaviors and the physician's evaluation of symptoms using special instruments (*16*). These instruments are divided into screening tools and diagnostic evaluation tools depending on their functions (Table 1) (*19*). Most of these instruments are of foreign origin, translated, and revised, so the translations may be biased. More importantly, the applicability of these instruments to China needs to be confirmed. Encouragingly, the level of primary care for ASD has improved with the gradual standardization of screening and diagnostic tools. A point worth noting is that the currently recommended diagnostic methods include information from a clinical assessment, the educational environment, and standardized tools rather than blindly accepting the diagnosis and implementing treatment (*20*).

4. Interventions commonly used in China

ASD has a complex etiology, and 75% of patients have additional neurological or psychiatric disorders, making treatment more challenging (*21*). Current therapies for ASD include pharmacological treatments and non-pharmacological interventions. Commonly used drugs

include antidepressants, atypical antipsychotics, and psychostimulants (*21*), which are limited to treating concomitant conditions rather than ASD itself (*22*). Traditional Chinese medicine interventions such as acupuncture, massage, and herbal remedies seem to have some effect on partial symptoms, but further research is needed to confirm these results (*21,23*). In contrast, behavioral and educational rehabilitation is an evidence-based intervention for core symptoms of ASD and is widely accepted for its demonstrable effects.

Interventions cited by the National Autism Center (NAC) in 2015 are domestic mainstream treatments for ASD (*24*). A survey of 1,136 Chinese rehabilitation facilities found that 57 interventions for ASD were used in China, the 3 most often used of which were behavioral interventions, language training and production, and natural teaching strategies. Others were complementary therapies such as traditional Chinese medicine and play therapy (*25*). Generally speaking, a wide variety of interventions are used in China, and the most common intervention strategy is to combine conventional rehabilitation training with other traditional adjuvant therapies.

5. Current status of rehabilitation and educational institutions for patients with ASD in China

At present, medical care for patients with ASD is supported by the government, including rehabilitation facilities belonging to the China Disable Persons' Federation (CDPF), research institutions, and public hospitals, as well as private rehabilitation and educational institutions (*26*). Although China's policy stipulates that children under 6 years of age with ASD can receive rehabilitation subsidies, the shortage of domestic rehabilitation therapists means that most doctors in public hospitals can only diagnose, evaluate, and advise patients rather than providing one-to-one rehabilitation training (*18*). Therefore, parents often choose rehabilitation and educational institutions for their expert quality services. However, a large proportion of these institutions are private organizations, and rehabilitation expenses of patients are mainly borne by patients' families instead of government subsidies, contributing to the heavy financial burden on families of patients with ASD (*18,26*).

With attention to ASD and improved policies for patients with disabilities, ASD education and rehabilitation in China has developed rapidly in recent years. According to data from the CDPF, 2,681 institutions provided rehabilitation services for people with ASD throughout the country by the end of 2020, and the number of staff and patients in these institutions has continued to grow (*27*). Nonetheless, there are still large gaps in service capacity between different institutions (*25*). As an example, daily training sessions can be conducted for up to 300 patients, but the minimum is only 8 (*25*).

6. Suggestions

China's capacity for primary care for ASD has generally tended to increase, and especially in the improved management of rehabilitation and education for patients with ASD (*27*). These changes will help to provide basic services to patients, rationally allocate national resources, and promote the standardized operation of institutions. But more needs to be done. An ASD screening and monitoring system needs to be created in accordance with the needs of Chinese patients as soon as possible; disseminating knowledge about ASD and enhancing psychiatrist training are essential to improving the early diagnosis of the disorder. In addition, ASD is classified as a mental disability in China, so national policies and subsidies are not directly targeted at patients with ASD but at the total population of patients with mental disabilities. Thus, more policies need to be implemented and funds need to earmarked for patients with ASD and autism research.

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Letter to the Editor

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Analysis of microsatellite instability using Promega panel in dermatofibrosarcoma protuberans

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SUMMARY Dermatofibrosarcoma protuberans (DFSP) is a rare neoplasm derived from fibroblasts. Although the frequency of microsatellite instability (MSI) in skin cancer is reported to be less than 5%, there is only one report of the status of MMR in DFSP. The only analytical report of microsatellite stability in which Promega panel is not used, showed that the frequency of MSI-high, MSI-low and microsatellite stable (MSS) cases was 13.9% (5/36), 16.7% (6/36) and 69.4% (25/36), respectively. Thus, the aim of this study was to evaluate the status of MMR in 36 patients with DFSP diagnosed at Kumamoto University. MSI analysis using the Promega panel showed that all cases were MSS, which indicated the absence of MSI in DFSP. This result indicates that the status of MMR may not be useful for the potential therapeutic application of pembrolizumab and the pathogenesis of DFSP may not involve MSI.

Keywords microsatellite instability (MSI), dermatofibrosarcoma protuberans (DFSP)

To the Editor,

The deficiency of DNA mismatch repair (MMR) indicates good therapeutic response to immune checkpoint inhibitors (ICIs). There are several methods to evaluate microsatellite instability (MSI), and the frequency of MSI occurrence in skin tumors is generally less than 5% (*1*). Promega panel (Promega, Madison, WA, USA) is approved as a companion diagnostic reagent for the administration of ICIs. There are few reports about the status of microsatellite stability in skin tumors evaluated by Promega panel, and no MSI-high tumors were detected in cutaneous angiosarcoma (*2*) and extramammary Paget's disease (*3*).

The pathogenesis of dermatofibrosarcoma protuberans (DFSP) is characterized by a fusion gene between the α-helix domain of the collagen type-1 gene (*COL1A1*) and the platelet-derived growth factor-β gene (*PDGFB*) (*4*). The only analytical report of microsatellite stability in which Promega panel is not used, showed that the frequency of MSI-high, MSI-low and microsatellite stable (MSS) cases was 13.9% (5/36), 16.7% (6/36) and 69.4% (25/36), respectively (*5*). However, there was no case study about the occurrence rate of MSI using Promega panel in DFSP. Thus, we investigated the status of MMR in 36 patients with DFSP diagnosed at our hospital.

A total of 36 paraffin-embedded sections were collected from patients with DFSP [aged between 19 and 69 years, 24 men and 12 women, all cases without metastasis] diagnosed at our hospital between 2001 and 2018. Isolation of genomic DNA, capillary electrophoresis, and the evaluation of MMR were conducted as described previously (*2*). Institutional review board approval and written informed consent were obtained according to the Declaration of Helsinki.

Capillary electrophoresis showed all 36 tissues as MSS. Our study presented three major considerable findings. First, the occurrence rate of MMR-deficient tumors among skin tumors (*1*) is less than 5%, which is consistent with the results of our study. Second, the absence of MSI-high tumors in DFSP indicates that MSI may have little relevance to the pathological mechanism of DFSP. Third, we investigated the status of MMR in DFSP using the Promega panel to evaluate the possibility of applying pembrolizumab therapy because Promega panel is an approved companion diagnostic reagent for the administration of ICIs. Our results suggested that MSI might not be appropriate for the determination of the administration of ICIs in DFSP. Investigations of tumor mutation burden (TMB) in DFSP may be necessary because ICIs are also approved for TMB-high solid tumors by Food and Drug

Administration. In conclusion, our study revealed that the DFSP is an MSS tumor.

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