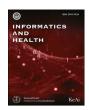
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Technological advances in out-of-hospital care: Digital solutions, Asia Pacific experiences, and inherent challenges

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ABSTRACT

The healthcare systems in the Asia-Pacific region are confronted with immense challenges due to an aging population and its rising demand for medical services. Out-of-hospital care supported by digital medical technology has emerged as a potential solution. Countries in the Asia-Pacific region are actively exploring the use of innovative digital technologies to develop out-of-hospital care programs tailored to each nation's context. However, there are also many non-technical challenges like technology maturity, qualification of healthcare staff, incentives of physicians within hospitals, funding and reimbursement, which inhibit the adoption of out-of-hospital care in four countries in the Asia-Pacific region: the United States, Australia, Singapore, and China. It proposes a practical technical catalog of out-of-hospital care, analyzes existing development challenges, and offers recommendations based on international best practices. Moving forward, it's urgent to further integrate technologies and the health system, and navigate multi-stakeholder collaboration in out-of-hospital care.

Introduction

Comprehensive chronic diseases and population aging have raised concerns about the continuum of care (CoC), which comprises preventive care, early detection, diagnosis, treatment, rehabilitation, and palliative.¹ CoC demonstrated significant advantages in reducing hospitalization, ² clinical outcomes, ³ and quality of life.⁴ As a new way to implement CoC, out-of-hospital care is an alternative to traditional in-hospital care, and delivers hospital-level medical services in non-hospital settings like homes, schools, workplaces, or general practices. It comprises two major types: early supported discharge (ESD), and admission avoidance (AA), of which the programs include home care, early discharge, clinical unit models among other forms.⁵ There are two key characteristics of out-of-hospital service⁶: (1) it could substitute acute hospitalization; (2) it could provide a level of quality of care comparable to that provided in hospitals according to disease severity.

The development of the out-of-hospital clinical model is of great

clinical and practical importance in the context of an aging population with rising demands for healthcare, rapidly increasing healthcare expenditures and a growing shortage of hospital beds and healthcare staff. In a prospective randomized controlled trial of an Italian home hospital program over six months,⁷ it was found that elderly patients with severe chronic obstructive pulmonary disease (COPD) who received inpatient care at home had significantly lower readmission rates than those receiving only general inpatient services (42% vs 87%, p < 0.001). Moreover, patients receiving home-based inpatient services reported improvements in quality of life and depression. Results from the use of the homecare model developed at Johns Hopkins University showed that patients receiving homecare services had an average of 19% lower health care costs and higher patient satisfaction compared with inpatients with similar disease severity.⁸

As one of crucial components of the continuum of care,⁹ information and technologies facilitate the treatment and make the current care appropriate for each individual. The good use of technologies such as

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out-of-hospital dialysis,¹⁰ cardiovascular and glucose monitoring,¹¹ and home-based rehabilitation system¹² is conducive to the rehabilitation of patients with various chronic diseases. In the response to the COVID-19 pandemic, home rehabilitation for patients with asymptomatic and mild infections sought for care from Internet-based medical services, such as teleconsultation and online prescribing.^{13–15}

Despite the apparent benefits and increasing utilization of out-ofhospital care, significant gaps in knowledge and implementation still exist, particularly in relation to adapting and scaling the model within varying policy contexts and health systems. In this review, we described the development, technology solutions, and further challenges for outof-hospital care in four distinct policy contexts: the United States, Australia, Singapore, and China. This paper aims to highlight the digital implementation of out-of-hospital care in the Asia-Pacific region and contribute to care and related industries.

Out-of-hospital care in Asia-Pacific countries

Table 1 shows the differences between out-of-hospital and inhospital care in patients, evaluation, treatment and operation. Considering the representativeness of out-of-hospital implementation and data availability, we selected typical cases in the United States, Australia, Singapore and China, with all information searched from peer-reviewed researches, public reports and government documents. The development of healthcare systems in four countries is presented in Table 2.

The United States

Although research on out-of-hospital care in the United States began in the 20C, their widespread adoption remained slow due to various reasons until the outbreak of COVID-19 when the Centers for Medicare & Medicaid Services (CMS) began allowing Medicare beneficiaries to opt for HaH programs. In 2020, CMS implemented the "Acute Hospital Care at Home" initiative, paving the way for Medicare to cover inpatient services at home. The public health emergencies coupled with the CMS response, led to a surge in demand for HaH services.

Fig. 1 illustrates the schematic and relevant technologies of the "hospital-at-home" program in the US, showcasing the Continuum of Care in out-of-hospital settings.¹⁹ Eligible patients are screened using validated scoring systems²⁰ and admitted to the out-of-hospital care process, after which they will receive treatments and frequent visits from a general internist and a registered nurse. Healthcare team members can be consulted via telephone, encrypted video, and encrypted short message service. The fundamental medical facilities are provided at home, including respiratory therapies, intravenous medications, in-home radiology, and point-of-care blood diagnostics (such as Abbott

Table 1

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The difference between	out-of-hospital care	and in-hospital care.

The difference b	etween out-or-nospital care an	iu ili-liospital care.
	Out-of-hospital care (Focusing on healing dysfunction, improve functional quality through improvement and compensation)	In-hospital care (Focusing on disease treatment, removing the cause, saving lives, reversing pathology)
Treatment	People with functional	People with all kinds of
Object	disorders and disabilities	diseases
Treatment Site	Rehabilitation medicine	Clinical departments of
	department, rehabilitation center, community, family	hospitals at all levels
Therapeutic Approach	Non-drug treatment, strong patient engagement	Medication and surgery
Behavioral Pattern	bio-psycho-social model	Biological and physiological driven
Evaluative	Physical, psychological, life,	Disease diagnosis, system
Criteria	and social functions	function
Working	Teamwork	Division of labor based on
Pattern		specialization

Table 2

	The United States	Australia	Singapore	China
% of GDP of the health sector	18.8	10.7	6.1	6.5
% of health expenditure	39	70.6	52.4	27.4
assumed by public funding				
% of health service provider	12	14.4	28.7	44.9
assumed by public				
organizations				
Life expectancy	76.4	83.3	84.9	78.2

Data are from World Bank Open Data,¹⁶ National Health Commission of the People's Republic of China,¹⁷ and Australian Institute of Health and Welfare.¹⁸

Laboratories). Vital signs of patients are monitored continuously using a small skin patch (such as VitalConnect) and reviewed by physicians and nurses on their smartphones.²¹ Finally, primary healthcare institutions will be responsible for the discharged patients.

By July 2021, eight months after the initiative's implementation, more than 66 home-based healthcare services provided by 140 hospitals received CMS approval. A remarkably 800,000 people were covered by Medicare in 2019, the majority of whom were beneficiaries of the home hospital model.²² The success of the U.S. Hospital at Home programs could be attributable to several factors. First, the program places demand on healthcare providers and medical staff. Physicians are required to assess and screen medical and non-medical factors before patients are transferred from the hospital to home. Only patients discharged from an emergency or inpatient unit are eligible for the program, and must undergo daily assessments by nurses, either in person or remotely. In addition, hospitals are required to report the quality and safety data of their HaH service to CMS.

The scalability of this HaH model presents several significant challenges. Despite the rapid expansion of HaH program, the number of hospitals offering this care remains low, with only 245 hospitals waived by CMS as of 2022.²³ Many patients are also unaware of this care option. A potential remedy is to amplify exposure to potential patients and healthcare providers, and bolster patient outreach initiatives. Second, achieving cost efficiencies should be taken into consideration. The treatment at home requires multiple physician and nurse practitioners to frequently round on patients and provide care, with extra traffic or communication costs. Evidence suggested that the length of hospitalization was longer when it took place at home, compared with in-hospital patients.²⁴ Furthermore, strict inclusion and exclusion criteria for selecting the appropriate patients are needed. Disease-specific validated risk classification scoring systems play a crucial role in screening HaH candidates,²⁰ particularly as critically ill individuals are unsuitable for home care. And the patients' socioeconomic factors are also properly reviewed.2

Australia

In Australia, out-of-hospital care is primarily represented by the use of home monitoring devices or technologies. By optimizing treatment pathways and leveraging medical technology, patient selfadministration, and remote monitoring devices. Australia has managed to reduce the in-hospital component of health care. This strategy has proven effective in increasing efficiency, enhancing patient outcomes, and decreasing hospitalizations in a variety of ways.

HaH is a major concept of out-of-hospital care. However, private clinics have also become integral to this care model, especially amid the COVID-19 pandemic. These private clinics offer more convenient care access, serving as an extension of in-hospital emergency services, thereby liberating patients from the confines of traditional hospital settings. For example, advancements in hip replacement technology allow patients to regain mobility shortly after surgery and return home within a day. Disease management also benefits from out-of-hospital

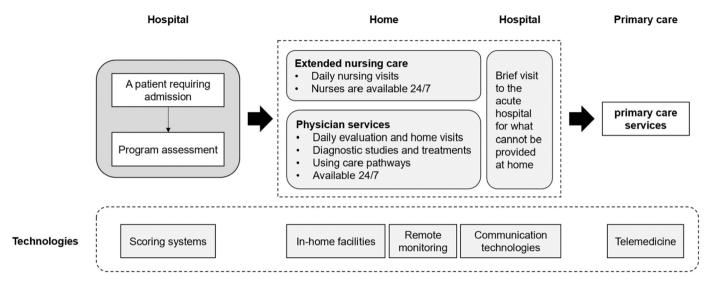


Fig. 1. The way of Hospital at Home programs work.

care and relevant technologies. The management of kidney disease in Australia is such a case. In 2004, the Western Australian Department of Health released a white paper, detailing the future management of kidney disease. In 2005, the Department issued a seven-year contract for two stand-alone satellite units and established a statewide home dialysis program. This program depends on Home Hemodialysis (HHD) and Continuous Ambulatory Peritoneal Dialysis (CAPD), which are easy to install and can be independently operated by patients at home.^{25,26} However, appropriate patients require training in a hospital setting, including exams and credentialing.

The Australian government is encouraging private health insurance purchases through the tax system, leading to a collaborative effort among private insurance companies and public hospitals to optimize procedures and reduce costs. While the government does not dictate specific procedures, there is a growing trend toward the HaH model.

Singapore

Digital technologies have become pivotal in Singapore's out-ofhospital medical services, with telemedicine and artificial intelligence (AI) technology being particularly well applied. In recent years, especially since the outbreak of the COVID-19, the use of virtual clinics, AIassisted treatment and home monitoring has significantly increased in Singapore. A notable instance is the application of telemedicine and AI in diabetic retinopathy screening. Diabetic retinopathy (DR), a condition caused by diabetes that damages the microvasculature of the eye, can impair vision and even lead to blindness. The Singapore Diabetic Retinopathy Screening Project (SiDRP) utilizes tele-ophthalmology for nationwide screening of 120,000-150,000 diabetic patients (50%) in 19 community hospitals.²⁷ By integrating telemedicine, AI, and medical technology, Singapore has effectively managed out-of-hospital diabetic retinopathy care. This approach has not only relieved hospital pressure but also reduced waiting time, improved patient experiences, and cut government spending.²

In addition to integrating telemedicine with AI, the Ministry of Health (MOH) is also actively promoting the piloting of the hospital at home model in Singapore, drawing inspiration from more mature implementations in the Europe and the U.S. In 2017, MOH adopted the "Beyond Hospital to Community" concept to guide the direction of national healthcare policy reform.²⁸ In April 2020, the MOH Office for Healthcare Transformation (MOHT) led the development of Singapore's HaH pilot program, based on the ideas of the Europe and the United States. The National University of Singapore Medical Group (NUSMG), in collaboration with the National University of Singapore (NUS),

launched a cohort study on the effectiveness, feasibility, and processes of the hospital at home model in the context of the COVID-19 pandemic.²⁹ Unlike HaH program in the United States, NUHS@Home has recruited therapists to join the medical team, and will be under the clinical governance of Division of Advanced Internal Medicine at NUH. The two-year study aims to determine whether this model, which is well established in the Europe, the United States, and Australia, can be adopted and popularized in Asian countries. To date, this study has granted more than 2000 Singaporeans access to clinical services at home.³⁰

China

The Chinese government has prioritized the establishment of a telemedicine system to address the uneven distribution of medical resources. In 2014, the government issued the Opinions on Promoting Telemedicine Services in Medical Institutions. Following the release of the 13th Five-Year Plan in 2016, telemedicine was integrated into major informatization planning projects, and industry standards for telemedicine were developed. By 2030, telemedicine is projected to be available across medical and health institutions at the provincial, municipal, county-level and rural levels. Currently, telemedicine services are mainly B2B (Business-to-Business) oriented, while Direct-to-Consumer (DTC) services, which would allow hospital doctors to communicate directly with patients, still requires improvement. Despite being viewed as the future of telemedicine,³¹ the DTC model is underdeveloped due to shortcomings in the medical insurance system. The reimbursement of outpatient telemedicine in Michigan ranges from 0% to 67%,³² while the medical insurance reimbursement standards in China haven't been unified, and the coverage is still incomprehensive.

In addition to this, China recognizes the crucial role of AI in healthcare. To support the development and application of healthcarerelated AI technologies, the government has released directives such as the Guidance on Promoting and Regulating the Development of Health Care Big Data Applications (2016), the 13th Five-Year Plan for Health and Health Science and Technology Innovation Special Plan, and the Guide for the Development of the National New Generation Artificial Intelligence Standard System.

Chronic disease management is also a central concern for China's out-of-hospital medical service system. For example, during Shanghai's fight against the COVID-19 pandemic, the Shanghai Renji Hospital, accredited for home hemodialysis since 2018, successfully assisted four home-hemodialysis patients during the lockdown. Internet-assisted home monitoring of patients' health allowed the hospital to save lives at a crucial time, demonstrating the potential of out-of-hospital medical services. However, the majority of China's funding and medical resources are still allocated to hospitals, and the investment in out-ofhospital rehabilitation care is insufficient, indicating a need for further development.

In the context of China's unique situation, out-of-hospital medical care include the following types of services: various types of medical or paramedical services, including active treatment, symptomatic treatment, palliative care, rehabilitation and health care, provided by professionals or certified patient self-providers in various settings outside of traditional hospitals, including community health centers, senior living facilities, professional rehabilitation facilities, homes, etc (Table 3).

A practical directory of technologies for out-of-hospital care in Asia-Pacific region

In summary, these solutions can be roughly divided into Screening / Diagnostic Products/Technologies, Intervention and treatment Products/Techniques, health Monitoring Management Products or Technologies. Selected case examples of technologies that support out-of-hospital care are listed in Table 4.

Among the examples in Table 4, AI plays a crucial role in health screening and diagnosis. Technology solutions has enabled the improvement of full life-cycle healthcare services. For example, the digital diagnostic product AegisPOC lies on an open web-based platform to integrate POC devices with laboratory information systems (LIS), health information systems (HIS), electronic medical records (EMR), quality management, user management and other systems, by which the quality and efficiency of diagnosis will be improved remarkably. Glaucoma is one of the leading causes of irreversible blinding eye disease.³³ The disease is characterized by structural changes in the optic disc, defects in the optic nerve fiber layer and visual field defects.³⁴ Glaucoma diagnosis is still affected by doctors' subjectivity, especially in early glaucoma detection; meanwhile, the distribution of medical resources in China is quite uneven, and the level of glaucoma diagnosis and treatment in primary hospitals is unsatisfactory and varies greatly.³⁵ In this context, AI product for glaucoma detection via fundus imaging to assist in screening and diagnosing early glaucoma and was granted a medical AI Class III medical device registration certificate in 2021.³⁶ Based on Tencent's deep learning technology, the system learns and analyzes data from tens of thousands of fundus photos to provide recommendations for clinical triage, and the application scenarios can be extended to hospitals, mass screening programs, population-based screening for glaucoma and pharmacies, community health centers, etc. Similarly, the deep learning system called Singapore Eye LEsioN Analyzer (SELENA+) is embedded in the national level eye screening program for diabetic patients. It analyzes eye retina images to indicate diabetes retinopathy and other aging-related eye diseases.²⁸ At the end of 2021, Shukun Technology signed a strategic cooperation agreement with the leading preventive medicine company Meinian Health Group in Beijing, and both parties plan to start in-depth cooperation around early screening of chronic diseases and health management. As the cooperation continues, AI projects such as "Heart and Lung Screening" have been deployed in hundreds of health checkup centers nationwide and have made great progress. It is understood that AI projects such as "Heart and Lung Screening" of Shukun Technology have been deployed in hundreds of health checkup centers nationwide.

Intervention and treatment solutions also prove to be very important for managing chronic diseases. ResMed focuses on out-ofhospital/home treatment solutions for chronic respiratory diseases such as obstructive sleep apnea (OSA) and chronic obstructive pulmonary disease (COPD), including Continuous Positive Airway Pressure (CPAP) and related telemedicine services (AirView cloud platform). CPAP is currently the gold standard for OSA treatment in international and domestic clinical medicine, and an indispensable treatment option for COPD patients in the acute phase so that their quality of life can be improved. Application scenarios include home, community health centers, and specialized institutions such as nursing homes and rehabilitation centers. Home hemodialysis treatment has been carried out in many countries in Europe and the United States as early as the 1950s and has been successful, greatly reducing the inconvenience of travel and the risk of infection for hemodialysis patients. In 2019, the U.S. government signed an executive order to encourage the development of home dialysis, while the technology in China is only widely distributed in hemodialysis centers and specialized hospitals. All of these prove that home hemodialysis is a treatment modality worth promoting. Patients with some self-care skills who are trained to perform home hemodialysis will greatly reduce the risk of cross-infection and improve their quality of life. This would be the best protection for patients, healthcare professionals and the public. A more easy-to-adopt case might be in the outof-hospital glucose management field. Medtronic's MiniMed™ 670 G System Hybrid Closed Loop System was recognized as one of the 25 most outstanding innovations of 2016. Both the ADA (American Diabetes Association) and EASD (European Association for the Study of Diabetes) cited it as the first choice for type 1 diabetes treatment. The Hybrid Closed Loop System makes diabetes management more effective and efficient and increases the benefits for patients with type 1 diabetes, hospitals, healthcare professionals and society. The Smart Guard technology embedded in the system helps measure a user's blood glucose level every five minutes, delivering insulin or suspending insulin injections based on real-time personalized needs. In addition, the technology reduces the incidence of hypoglycemia, related complications, and healthcare costs.

Monitoring and management tools are important means to improve patients' prognosis. Roche Diagnostics' CoaguChek promotes the convenience and accuracy of coagulation monitoring conducted by patients. Abbott's Freestyle Libre Glucose Monitoring System changes the traditional way of glucose measurement, realizes "measuring blood glucose without sticking your finger", and opens a new era of digital management of "glucose measurement with one scan on the phone". It is connected with the application through the smart sensor "small wafer". It can be used continuously for 14 days, helping users to get real-time

Table 3

The comparisons of out-of-hospital care in four countries.

	The United States	Australia	Singapore	China
Application areas	Hospitals approved by CMS	Vary in different states	Nationwide	Mainly public and private hospitals
Specific measures	HaH programs	Private clinic care / Home hemodialysis	SiDRP	Telemedicine
Characteristics	Continuous care	Private organizations involvement	AI-centered	Business to business
Advantages	Stringent regulationsReimbursed by Medicare	Well experiencedPublic-private cooperation	Increase screening efficiencySave the labor cost	Government supportPublic-private cooperation
Disadvantages	 Extensive awareness Cost efficiencies Selecting the appropriate patients 	 Increase cost to patients Housing problems (shortage and water quality) 	 False-positive results Integration of AI and healthcare 	Reimbursement standardsPoor direct-to-consumer

Table 4

A practical dire	ectory of technologies for out-of-hosp	ital care.
Service category	Product Profile	Country
Screening and	 The digital diagnostic product AegisPOC is an open web-based plat- form. It connects POC equipment in hospitals and clinics with labora- tories', grasp information from mul- tiple sources, and presents the results 	Global
	 in an appropriate format. Tencent's AI product for glaucoma detection makes use of fundus recognition technology for auxiliary diagnosis, and applied in hospitals, primary healthcare institutions and screening programs. 	China
	 SELENA+ analyzes eye retina images to sign three types of diabetic related eye diseases: diabetic retinopathy, glaucoma, and age-related macular degeneration. 	Singapore
	 The AI heart-lung screening project of Shukun Technology have begun to be deployed in hundreds of physical ex- amination centers across China. Cus- tomers can use the products to find their disease risks early. and treatment 	China
	ResMed's one focus is on out-of- hospital/home treatment programs for obstructive sleep apnea (OSA), chronic obstructive pulmonary dis- ease (COPD) and other chronic res- piratory diseases, including home positive airway pressure non-invasive ventilator (CPAP) and related remote digital medical services (AirView cloud platform).	Global
	 Fresenius Medical Care innovatively uses NxStage System One to realize homehemodialysis, which is easy to use, helps patients better return to their families and society, and improves their quality of life. 	Global (excluding some European countries and China)
	The main business of Wego Blood Purification Industry Group covers the whole industry chain of hemodialysis. In 2011, it undertook the pilot task of the independent hemodialysis center of the Ministry of Health.	China
	 The latest generation of MiniMed[™] 670G is regarded as the first choice for T1 diabetes treatment. The Smart Guard technology embedded in the system can help measure blood sugar level every five minutes and provide insulin or suspend insulin injection according to real-time personalized needs. 	USA and Europe
-	nd management	
	 Roche Diagnostics' CoaguChek is a medical device that provides coagulation monitoring and management for patients using warfarin, which can increase the anti- coagulation monitoring compliance rate (TTR) by 27.5%, thereby reducing the occurrence of compli- cations such as thromboembolism and severe bleeding. 	Developed countries including EU, USA, Canada, Australia and Japan
	 Abbott's instantaneous scanning glucose monitoring system changes the traditional way of measuring glucose and realizes blood glucose 	Global

Informatics and Health 1 (2024) 9-15

Table 4 (continued)

Service category	Product Profile	Country	
	measurement without pricking fingers, and starts a new era of digital management by measuring blood glucose with a scan of a mobile phone.		

glucose value, glucose change curve and historical information easily anytime and anywhere, supporting diabetic patients and doctors to carry out convenient and scientific glucose management.

Apart from the solutions, it is also worth deep dives into the scenarios for these technologies to play a role. Supplementary Table 1 summarizes some examples of scenarios/settings in which these technologies are applicable in China.^{37–41}

Challenges of out-of-hospital care

Countries in the Asia-Pacific region are actively developing models of out-of-hospital care to suit their unique national circumstances. The future of out-of-hospital care lies in technical and non-technical challenges in the following areas:

Qualification of Healthcare Professionals: Out-of-hospital care necessitates the establishment of well-qualified, comprehensive teams of health professionals, including doctors, nurses, rehabilitators, and other medical staff. Specialized training programs, as well as standardized management and assessment systems, should be implemented to ensure high-quality care.

Patient and Technical Equipment Qualification: Providers of home healthcare services should classify patients based on their conditions and needs, and assess patient eligibility for home health care. It's crucial to provide personalized medical and nursing services to prevent the misallocation of medical resources. Further studies focusing on patient demand, application scenarios, and requirements for out-ofhospital care are encouraged.

Technology and Device Solutions: Specific technologies and products suitable for home use, like hemodialysis machines, need to be identified and promoted. A comprehensive list of available technologies and products for home healthcare should be developed.

Recognition of Healthcare Workers' Labor Value: It's essential to coordinate multiple parties' interests within the out-of-hospital care system to ensure hospitals and healthcare workers' interests are not compromised. This could involve creating awareness around key chronic diseases, developing application management norms, establishing a review and approval system, and forming service compensation mechanisms for home hemodialysis products and technologies.

Reimbursement Coverage: Future reimbursement policies should aim to cover the entire course of health care, with commercial insurance playing a crucial role in developing a diversified payment system. The proposed four-dimensional cooperation mechanism, encompassing product linkage, smart health insurance management platforms, improved governance mechanisms, and the joint creation of new product plans, could pave the way for a more inclusive and efficient out-ofhospital care system.

Homecare of Supply chain: Traditional hospital supply chain starts from manufacturers and ends up with stock in care units.⁴² Out-of-hospital care has expanded the boundaries of healthcare services to patients' home, which requires necessary medical equipment and products. Compared with hospital care, the supply of out-of-hospital care has the characteristics of multiple product types, small lot and personal demands. It's crucial to focus on the infrastructure, improve medical supply chain of out-of-hospital care, and integrate digital schemes into logistics activities.⁴³

Limitations

This review has limitations, such as differences in healthcare systems across Asia-Pacific countries and lack of extensive patient perspective exploration. Therefore, the recommendations put forth in this paper, while beneficial, may not be universally applicable or optimally effective in every context and population.

Conclusion

Out-of-hospital care surpasses the constraints of traditional inhospital models, transferring healthcare scenarios from within hospital walls to more accessible out-of-hospital settings. The application and promotion of out-of-hospital medical care, especially the digital application, has emerged as a major global trend to enhance medical continuity. Policymakers in the Asia-Pacific region need to explore further to find suitable technical and non-technical paths for their own unique circumstances.

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CRediT authorship contribution statement

You Wu: Conceptualization, Methodology, Supervision, Writing – review & editing. Li Zhang: Conceptualization, Data curation, Methodology. Zeqi Liu: Methodology, Validation, Visualization, Writing – review & editing. Kai Mo: Formal analysis, Investigation. Wenting Pu: Writing – original draft, Writing – review & editing. Jiali Yin: Resources, Writing – original draft. Ziyu Ma: Writing – review & editing. Zhuocheng Jiang: Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

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L. Zhang et al.

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