An Impact Evaluation of Clinical Pathways Management for Cerebral Infarction in a Rural Area in China

By

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

INTRODUCTION

Given the challenge of addressing a growing non-communicable disease burden with limited health resources in developing countries, clinical pathways (CP) have been proposed as a strategy to optimize resource allocation in a climate of increasing healthcare costs. Ongoing reforms to China's county-level public hospitals have generated an interest in developing evidence-based CP with a focus on controlling unreasonable medical costs, while at the same time raising the overall quality of healthcare services provided. An intervention project of evidence-informed CP on two selected disease areas (chronic obstructive pulmonary disease (COPD) and stroke) was conducted by China National Development Research Center (CNHDRC) in 2014. Since then, the implementation of CP project has received significant government interest, and has been seen as a model for replication across the country by the national health authority. However, the real impact of CP intervention in the short and long term is not yet clear. Therefore, an impact evaluation was considered necessary to identify the effectiveness and cost-effectiveness of implementing the CP in the pilot setting before being scaled up in other parts of the country and for other conditions.

Stroke incidence has declined by over 40% in the past four decades in high-income countries, but over the same period, incidence has doubled in low and middle-income countries. Taking cerebral infarction (CI, a type of stroke) as an example, this study aims to understand the impact of the CP intervention on treatment effectiveness, and the use of resources in both short and long term. The study not only adds valuable evidence to the literature of CP management of CI, but also seeks to demonstrate the potential effectiveness and cost-effectiveness of CP intervention in the real setting of

rural China taking into account contextually appropriate solutions to enable continuous improvement in intervention effectiveness.

LITERATURE REVIEW

A literature review focusing on effectiveness and cost-effectiveness of CP in management of in-hospital CI patients was undertaken by thesis author and a second reviewer, using a number of key databases (PubMed, Medline, Embase, Cochrane library and CINAHL) applying pre-defined keywords and subject headings. The Cochrane collaboration's tool for assessing risk of bias was used to document the internal validity of individual studies. In addition, forest plots of selected outcomes across different studies were performed where heterogeneity was not judged to be a concern. Since there are high levels of variation in the nature of the disease and treatment depends greatly on local circumstances, the application of CP in management of in-hospital CI patients in the studies reviewed reveals conflicting evidence given the variety of settings studied, the diversity of aims, and variation in reporting outcomes. Some studies reported that the introduction of CP for a broad range of conditions can reduce the length of stay (LOS), in-patient complications, and total costs of acute hospital admissions while maintaining quality of care, improving patients' outcomes, interdisciplinary cooperation and staff satisfaction. Conversely, there are studies reporting no or minimal measurable benefits regarding LOS, readmission to hospital, mortality rates and total costs, and no positive "return on investment". Overall, the result of literature review does not provide a clear justification and firm conclusion for the implementation of CP for hospital-based CI management. A larger population scale study assessing the effectiveness and cost-effectiveness of CP is needed.

METHODOLOGY

The study analysis was performed using quantitative data collected from a pilot site-Hanbin county (in Shannxi province of China). First, descriptive statistics of the entire dataset and of selected subsets were provided, and data were examined to see if outcomes were distributed normally. Next, three major type of analysis were processed, namely: difference in difference (DID) after propensity score matching (PSM); interrupted time series (ITS); and Markov modeling. DID study design is commonly applied to evaluating observational data in order to address the problem of time-dependent trends in outcomes unrelated to the policy change, and PSM can balance the variation of patients' characteristics using matching skills. ITS is an intuitive, practical and powerful analytical approach which is used here for evaluating longitudinal effectiveness of a time-limited intervention before and after a specific time point, using routinely collected longitudinal data. In terms of the ITS analysis, overall intervention effectiveness, based on a number of outcomes, was explored over a period covering 12 months before the intervention was introduced, and 36 months after the intervention was performed. For both the DID and ITS analysis, the primary outcomes of total hospitalization expenses and its components (medication expenses, radiology expenses, laboratory test expenses, diagnostic expenses and consultation expenses), LOS and utility value were analyzed. The Markov model is a routinely analytical tool in cost-effectiveness to simulate the disease trajectory and compare the relative costs and outcomes of an intervention against a relevant alternative. In this study, two Markov models were developed to identify the cost-effectiveness of CP management for patients admitted into hospital and discharged after CP management. Estimations of the incremental cost-effectiveness were generated, supported by

comprehensive sensitivity analysis. Ethical approval was obtained from the University of Waterloo Research Ethics Committee (ORE#22396) for this research.

RESULTS

After several rounds of screening with specified selection criteria, 2,533 CI patients' records were obtained and grouped into 4 subgroups. DID analyses result shows the impact of CP intervention is generally positive after removing potential confounding factors using PSM. Total hospitalization cost decreased, as did LOS, while European Quality of Life Scale-5 dimensions-3 Levels (EQ-5D-3L) based utility value increased. For ITS, the general tendency is similar for all primary outcomes. Results show that CP implementation slowed down the rate of increase of costs and LOS. However, most of the parameters were not statistically significant based on t-tests.

For the Markov model-based cost-effectiveness analyses, the impact of CP intervention was observed to be not cost-effective in short term (21 days), but appeared to be cost-effective in long term (lifelong). For patients who are at stage of hospitalization, CP intervention of CI patients was not cost effective, and the ICER value was higher than the pre-defined threshold. However, the intervention of CP led to better health-related quality of life as indicated by higher utility value. For patients who are at the stable stage, namely being discharged by hospital, CP intervention of CI patients was the dominant strategy, whose ICER was much lower than the pre-defined threshold. In conclusion, combing both acute and stable stages, the CP intervention is cost-effective as ¥30,071.79/QALY with higher costs and Quality-adjusted life year (QALYs), comparing to the 1 time local GDP in 2014 (¥46,929.00/QALY).

DISCUSSION

In the literature, the application of hospital-based CP in management of acute stroke CI is associated with positive and negative effects, but this study reported more likely positive results in terms of selected primary outcomes and cost-effectiveness. The impact of the intervention could not only be attributed to the application of CP itself, but also its integration with awareness of standardized treatment among clinical practitioners, extensive training and support, and incentive management approaches. All these were combined with extensive stakeholder engagement given the ongoing China's nationwide healthcare reform. It is clear and significant that the perceived importance of using evidence to inform practice has changed. But results of DID and ITS analysis should be regarded as provisional and a complex causal chain requires further investigation over a longer time period, with the collection of additional data. Development of the Markov model was a means to assess the long term effectiveness and cost-effectiveness of such a complex intervention to support evidence-based decision making. Much more can still be done in re-directing resources away from the county hospital sector towards community care in rural China. Further refinement is also possible using information technology innovations, including electronic pathways plug-ins into clinical decision support and patients' health record systems, that can better monitor baseline activity and link compliance with preferred activities to appropriate reimbursement. The strength of the study is in applying statistical skills of DID, PSM, ITS and Markov model in analyzing the impact of CP effects. The limitation of the study is identifying confounding factors in explaining the casual chain between intervention and observed primary outcomes.

CONCLUSION

The evaluation findings and lessons learned from the pilot will be widely discussed and disseminated to policy-makers to enable evidence-based decision-making for CP implementation in China.

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Last but not the least, I would like to thank my family, for all the love and support throughout writing this thesis, especially on the most stressful of nights. I dedicate this labor of love to my daughter—Ruiying Guo, who has inspired me throughout my post-graduate academic journey.

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List of abbreviations

(a)OR	(adjusted) Odd Ratio
(a)RR	(adjusted) Relative Risk
A&E	Acute and Emergency
ADL	Ability in daily living
ASU	Acute Stroke Unit
BI	Barthel Index of activities of daily living
CC	Conventional Care
CCDC	China Center for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	Cerebral Infarction
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNHDRC	China National Health Development Research Center
COPD	Chronic Obstructive Pulmonary Disease
CP	Clinical Pathways
CPC	Communist Party of China
CT	Computerized tomography
CUA	Cost-utility analysis
DALY	disability-adjusted life years
DID	Difference in difference
EBM	Evidence-based Medicine
ECG	Electrocardiography
ECP	Emergency clinical pathway
EMS	Emergency medical service
EQ-5D-3L	European Quality of Life Scale-5 dimensions-3 Levels
EQ-VAS	EuroQoL Visual Analogue Scale
ER	Emergency room
ERI	Economic Reform Initiation
F-test	Fisher test
GBP	Great Britain Pound
GDP	Gross Domestic Product
GP	General Practitioner
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICD-10	International Classification of Diseases-10th Revision
ICER	Incremental Cost Effectiveness Ratio
ICH	Intracerebral Hemorrhage
ICP	Integrated care pathway
IQR	Interquartile range
ITS	Interrupted Time Series
ITT	Intention to treat

K-S	Kolomogorov-Smirnov
LOS	Length of stay
MCA	Ministry of Civil Affairs
MCHI	Maternal and Children Health Institution
MCS	Mental Component Summary
MDGs	Millennium Development Goals
MDT	Multidisciplinary team
Medline	Medical Literature Analysis and Retrieval System Online
MOF	Ministry of Finance
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Scale
MSU	Mobile Stroke Unit
NCD	Non-communicable Disease
NHC	National Health Commission
NHFPC	National Health and Family Planning Commission
NHSA	National Healthcare Security Administration National Healthcare Security Administration
NICE	National Institute for Health and Care Excellence
NIHSS	National Institute of Health stroke scale
NRCMS	New Rural Cooperative Medical Scheme
OLS	Ordinary Least Square
OOP	Out-of-Pocket
OWSA	One-way Sensitivity Analysis
PCS	Physical Component Summary
PoC	Process of Care
PP	Per-protocol
PRIMSA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSM	Propensity Score Matching
QALY	Quality-adjusted Life Year
RCT	Randomized Controlled Trials
SARS	Severe Acute Respiratory Syndromes
SF-36	Short form Health Survey with 36 items
SU	Stroke Unit
S-W test	Shapiro-Wilk test
TCM	Traditional Chinese Medicine
THE	Total Health Expenditure
TIA	Transient Ischemic Attack
tPA	tissue-type Plasminogen Activator
TTO	Time Trade Off
UERSMI	Urban Employees and Retiree Social Medical Insurance
UHC	Universal Health Coverage

URSMI	Urban Resident Social Medical Insurance
WHO	World Health Organization
WTP	Willingness to Pay
YLL	Years of Life Lost

Chapter 1 Introduction

Summary of Chapter

This chapter is divided into three major parts. The first part allows the reader to understand the general setting of the study by introducing China's healthcare system and healthcare reforms, with particular focus on rural China. The second part focuses on the introduction of stroke as the disease targeted by the intervention, describes clinical pathways (CP), the study intervention, to understand the effective mechanism of CP and, finally, summarizes evidence in international communities. In addition, CP for cerebral infarction (CI, a subtype of stroke) is emphasized and introduced. And, the CP intervention activities adopted in a pilot hospital in China are described and the purpose of the study is introduced.

Part one: China's healthcare system and healthcare reforms

1.1. China healthcare system

1.1.1. Overview of China

China is the third-largest country geographically, with 56 ethnic groups inhabiting, whose mainland population of approximately 1.4 billion, equivalent to 18.4% of the world's total (NHC, 2018). In the political context, China is a centralized administrative system under the leadership of the Communist Party of China (CPC). The administrative system has five tiers. In descending order, they are the State Council, provincial-level government (including minority autonomous regions, special administrative regions, and municipalities under direct central government control), city government, district or county government (in urban and rural areas respectively), and townships(in rural areas) and communities(in urban areas)(Policies, 2015).

In economic development, China experienced a planned economy phase similar to the Soviet Union, beginning with the birth of “new China” as founded by the CPC in 1949. In 1978, the central government started to implement the “Economic Reform Initiation” (ERI), which converted China to a socialist market economy. The transition of economic development brought a rapid growth and introduced change in every aspect of economy and society. Since the late 1980s, China has experienced rapid economic growth, with China’s real Gross Domestic Product (GDP) (Group, 2019a)growing at an average annual rate of nearly 10% from 1979 to 2017(Service, 2019). However, the income gaps between urban and rural areas, among regions, and between various groups of citizens, are widening(Policies, 2015).

In terms of where people lived, rural areas hosted the majority of the Chinese population, which is why China was recognized as an agricultural country. After 2012, the urban population outnumbered the rural population because rural migrants were rushing into cities for better job opportunities. By 2017, urban residents made up more than half of the Chinese population (58.5%)(NHC, 2018). In addition, the population of China is distributed unevenly, with higher density in eastern (relatively richer) areas and lower density on the (relatively poorer) western plateau. Moreover, China is facing a population aging problem. As of 2016, there were already 158.31 million people over the age of 65(Group, 2019b), approximately 11.39% of the population(NHC, 2018). In short, in the last three decades, China has experienced dramatic economic and demographic transitions in urbanization, industrialization, and large-scale migration. Consequently, the Chinese healthcare system and the population's health status were affected significantly.

1.1.2. Health status in China

In term of health status, the challenges of Chinese residents were changing from facing high birth rate, high death rate, low health spending, low health insurance coverage, and low life expectancy to tackling low birth rate, low death rate, expensive health spending, high health insurance coverage, and high life expectancy(Policies, 2015). The health status glance of Chinese residents in 2017 can be seen in

Table 1-1. Meanwhile, China's disease profile is shifting towards chronic disease due to economic, geographic and demographic (aging) transitions. Consequently, the healthcare system faces the challenge of transitioning from focusing on acute care and control of communicable disease to a system supporting prevention and rehabilitation stages and cost-effective management of non-communicable diseases. The disease risk factors related to lifestyle and social determinants have grabbed more attention from various stakeholders, including government and the general public. By 2016, the national authorities realized there was a need for an overall course management on healthcare rather than a focus on the treatment phase only. In 2016, the CPC Central Committee and the State Council released the "Healthy China 2030" blueprint, which covers areas such as public health services, environment management, the medical industry, food and drug safety, etc.(Xinhua). In recent years, "Healthy China 2030" was recognized as the national healthcare strategy for collection of all relevant resources towards improving the health status of Chinese and strengthening the healthcare system. In July 2019, the State Council announced a new national guideline proposing 15 special campaigns to intervene in health-influencing factors, protect full-life-cycle health and prevent and control major disease (ZX, 2019).

Table 1-1 Health status of Chinese residents in 2017

Description	Value
Birth rate	12.43‰
Mortality rate	7.11‰
Infant mortality rate	6.8‰
Life expectancy	76.7 years
Prevalence rate of chronic disease in 2013	330.7‰
Health Insurance Coverage rate	94.2327%

Resource: China health and family planning statistics yearbook 2018

1.1.3. China's healthcare system

To understand the China's healthcare system better, the relevant information can be considered in three related aspects: a health financing system, a health-service delivery system and a health supervision system (Policies, 2015).

1.1.3.1. Financing system

Healthcare is funded by the mix of general taxation, social insurance, private insurance, company-based health insurance schemes and out-of-pocket (OOP) payments. The total health expenditure (THE) is 5 trillion, 259.8 billion YUAN in 2017 (as a percentage of GDP it reached 6.36%), while OOP expenses accounted for 28.8% of THE (NHC, 2018). Although the OOP expenses has fallen from almost 60% in contrast to 2002, before rural residents were covered by a healthcare insurance scheme, the OOP rate is still higher than the government's expected goal, which is less than 20% of THE, as stated in the national healthcare strategy "Healthy China 2030"(Council, 2017). Controlling the cost burden on households is a policy priority (Long, Xu, Bekedam, & Tang, 2013; H. Zhang, Hu, Wu, Yu, & Dong, 2015).

At the time of the study, China operated three major healthcare social insurance systems: Urban Employees and Retiree Social Medical Insurance (UERSMI), Urban

Resident Social Medical Insurance (URSMI) and the New Rural Cooperative Medical Scheme (NRCMS). Each insurance scheme has disparate benefits packages, reimbursement rates and deductible amounts set at the city (UERSMI, URSMI) or county level (NRCMS), which vary due to differing levels of financing. Moreover, a medical financial assistance fund, paid for by the government and charitable donations, subsidizes premiums and OOP costs for those in financial need. The information for these insurance schemes can be found in Table 1-2.

Rates of health insurance coverage have increased rapidly in recent years. Between 2003 and 2011, insurance coverage increased from 30% to 94% and average share of reimbursed inpatient costs rose from 14% to 47% over the same time period (Meng et al., 2012). In some well-funded regions such as Beijing, specialized operations (e.g., organ transplants) and innovative drugs (e.g., anti-cancer drugs) are included (L. Li & Fu, 2017) in the benefit directory, with higher reimbursement rates. In general, spending on medicines accounts for the biggest share of insurance payments among the three major insurance schemes, about 43% of THE (WHO, 2011).

Table 1-2 Information of three major healthcare social insurances

Name	Enrolment	Typical benefits	Coverage (NO. of people)	Per-capita premium
UERSMI	Mandatory for workers in urban areas, financed by premiums paid by employers and employees	Expenses for inpatient services, at outpatient clinics, and designated pharmacies	303million	1666 YUAN
URSMI	Voluntary; financed by individual premiums and government subsidies	Covers similar expenses as UERSMI in each region	884million	930YUAN
NRCMS	Voluntary, financed by rural household	Covers inpatient and catastrophic	133 million	613.46YUAN

	premiums and government subsidy	outpatient expenses (general outpatient coverage depends in region)	

Resource: China health and family planning statistics yearbook 2018
Exchange rate: 1CAD=5.2 YUAN.

1.1.3.2. Supervision system

The healthcare rights of Chinese citizens are defined in China's constitution as follows: "Citizens of the People's Republic of China have the right to material assistance from the state and society when they are old, ill or disabled. The state develops social insurance, social assistance and health services that are required for citizens to enjoy this right" (Council, 2017). The health authorities of multi-level governments are responsible for all the healthcare issues within a particular territory, under the leadership and technical guidance of health authorities at higher levels.

At the time of the intervention, the supervision system was coordinated by the national health administration body called the National Health and Family Planning Commission (NHFPC), formerly the "Ministry of Health." The NHFPC was replaced by the National Health Commission (NHC) in 2018. Other ministries, including the Ministry of Finance (MOF), the National Healthcare Security Administration (NHSA, founded in 2018 to manage diversity healthcare insurance system nationwide), and the Ministry of Civil Affairs (MCA), have responsibilities relating to financial processes and the accessibility of healthcare services

Management of the healthcare system is delegated to mainland China's 31 provinces, municipalities and autonomous regions. Imitating the structure of the political management system, the health administration is organized in a hierarchy of four tiers, with NHFPC as the ultimate national healthcare authority (CNHDRC, 2015). Provincial, municipal and city or county health bureaus are the main

administrative bodies at the regional level and generally mirror the organizational structure of the NHFPC. These regional bodies are responsible for implementing plans within their local areas (Policies, 2015). Healthcare services are also delivered at the township health center and village clinics (in rural areas) and community healthcare facilities (in urban areas), but there are no independent administrative bodies (CNHDRC, 2015).

1.1.3.3. Healthcare delivery system

Similar to healthcare systems worldwide, the Chinese healthcare delivery system is divided into a medical services system and a public health system.

Medical services are delivered via various sizes of general hospitals, specialized hospitals, community or township healthcare facilities and village clinics. Ideally, the healthcare delivery system acts like a pyramid, in which a patient with minor or chronic diseases are managed through primary health care (community or township healthcare facilities and village clinics) and only acute and severe patients can be treated in hospitals with Acute and Emergency (A&E) and specialized professionals. However, the situation is the opposite in China. An integrated health care system composed of the primary healthcare system and hospitals sections is not yet well-established, and the dual patient referral mechanism between upper-level health institutions and lower-level health institutions is absent. There were 310,563 hospitals in China in 2017, of which more than 90% were public hospitals (NHC, 2018). Hospitals are the dominant supplier of medical services in the Chinese healthcare system. Patients normally choose to go to hospitals directly rather than going to primary care institutions, such as village clinics or township healthcare centers. Barriers to the use of primary medical care include a lack of trust in the quality of non-hospital care and limited access to primary care facilities for large sections of the

population. In addition, hospitals can offer both inpatient and outpatient services simultaneously, which is convenient for patients. In 2009, more than 40% of the population did not have ready access to primary care centers (H. Wang, Gusmano, & Cao, 2011). More importantly, the reimbursement rate, acting as an economic leverage, is not significantly different between primary and advanced healthcare institutions. Therefore, given the belief by people that hospitals are more advanced and provide better service, people flock to hospitals, which are consequently overcrowded. The medical service delivery system was described as an upside-down pyramid, which is the opposite of the normal system. Consequently, hospitals are the major providers of medical services and this is reflected by the concentration of funding and resources going into the hospital sector. In terms of hospital type, generally, hospitals contribute most medical services and consume most health funding. They can be defined as secondary or tertiary hospitals depends on what they can treat. Mental, maternal, child care, dental, oral and rehabilitation services can be provided by specialized hospitals, such as Maternal and Child Health Institutions (MCHI). And, every city and county has at least one traditional Chinese medicine hospital, which can provide herbal treatment, acupuncture and massage services (Policies, 2015).

Public services are handled mainly by the China Center for Disease Control and Prevention (CCDC), whose four-tier management systems are organized and managed in the method of the four-tier hierarchical healthcare management authorities. In addition, community healthcare centers, township health centers and village clinics provide public health services, in urban and rural areas respectively. The NHC launched basic essential public services for both urban and rural populations, such as chronic disease control, vaccination, the creation of health profiles and health

promotion (Policies, 2015). MOF is responsible for the financing of public health services through national general taxation. The per capita cost of the basic and essential public health service package was 55 YUAN in 2018 (Website, 2018). Since the outbreak of Severe Acute Respiratory Syndromes (SARS) in 2003, the government has invested huge resources to strengthen infrastructure development and the professional capacity of public health emergency responses.

Despite major achievements in terms of healthcare financial protection and accessibility, and meeting several key Millennium Development Goal (MDG) indicators, China has not reached universal health coverage (UHC) yet, and faces serious challenges preparing its health system to meet the population's rising healthcare needs and expectations (CNHDRC, 2015).

1.2. China rural healthcare system

Healthcare delivery in China is divided into an urban healthcare system and a rural healthcare system. The rural healthcare system provides for approximately 576.61 million people permanently living in rural areas, excluding the floating population that occasionally works in urban areas. This is approximately 41.5% of China's population (NHC, 2018).

The rural system is based on different levels of healthcare facilities:

- Village clinics, staffed by general practitioners, provide preventive and basic primary care services and do not offer inpatient services (Barber, Michael, Henk, & Jin, 2014).
- Township health centers accommodate primary care and limited specialized outpatient and inpatient services.

- County-level hospitals play a leading role in the local healthcare network, providing specialty care for both outpatients and inpatients, and referring patients as needed to advanced municipal and provincial hospitals.

The rural healthcare system is given fewer resources than its urban counterpart. There are less than half the number of beds per capita in rural areas compared with urban areas (3.11 per 1,000 people in rural areas vs. 6.88 in urban areas) (NHC, 2018) and much less than half the number of healthcare workers per capita (3.77 health care practitioners per 1,000 people in rural areas vs. 9.70 in urban areas) (NHC, 2018). Key information about the rural healthcare system at the time of the study is summarized in Table 1-3

Table 1-3 Facts of China's rural healthcare system in 2015

	Indicator	**Value**
Health Expenditure (annual)	National healthcare expenditure (% of GDP)	3,531.24 billion YUAN (5.55%)
	Total rural healthcare expenditure	802.4 billion YUAN
	Healthcare expenditure per capita	2,327 YUAN
	Rural healthcare expenditure per capita	1,274 YUAN
Healthcare Capacity	NO. of rural healthcare facilities	825,176
	NO. of county-level hospitals	12,365
	NO. of township healthcare centers	36,902
	NO. of village clinics	645,470
	NO. of beds in rural healthcare facilities	3,411,793
	NO. of beds per thousand in rural healthcare facilities	3.54
	NO. of beds in county-level general hospitals	2,051,612
	NO. of beds in township healthcare center	1,167,245
Volume of healthcare service (annual)	NO. of visits to county-level hospitals	626,004,112
	NO. of patients discharged from county-level hospitals	21,717,888
	Average LOS at county-level hospitals	8.1 days
	Outpatient visits to township healthcare centers	1,000,675,370
	Inpatient admission to township healthcare centers	37,326,053
	Inpatient discharge from township healthcare centers	37,130,133
	Average LOS at township healthcare centers	6.3 days
	Outpatientvisits in village clinics	1,800,452,987
Human resources	NO. of health professionals	5,453,652
	Health professionals per thousand residents	3.77

	NO. of Assistant doctors	1,460,827
	Assistant doctors per thousand residents	1.51
	NO. of Licensed doctors	1,044,095
	Licensed doctors per thousand residents	1.08
	NO. of Registered nurses	1,266,777
	Registered nurses per thousand residents	1.31
	NO of GPs in township healthcare center	432,831
NRCMS	Insured people	540million
	Per capita funding	490.3YUAN
	Total funding	302.528 billion
	No. of Reimbursements	1652.206 million
	Utilization rate of NRCMS fund	95.5%
Health status	Neonatal mortality	6.9%
	Infant mortality	10.7%
	Children under 5 years old morbidity	14.2%
	Maternal morbidity	22.2 per ten thousand
	Prevalence rate of chronic diseases	294.7%
Health account per capita	Average inpatient expenditure at county-level hospitals	6,359.9 YUAN
	Average medicine expenditure of each inpatient visit at county-level hospitals	2,427 YUAN
	Health expenditure per capita (% of consumption expenditure)	753.9 YUAN (9%)

Source: 2015 Statistical Yearbook for Health and Family Planning, NHFPC.
Exchange rate: 1CAD=5.2 YUAN.

Accessibility to health services for rural residents has improved in recent years since a new round of healthcare reform in 2009. The NCRMS covered approximately 800 million people and required a household premium of 305 YUAN in 2012 (Zhu, Zhang, Yuan, & Tian, 2016). Summary of NRCMS can be seen in Table 1-4.

Table 1-4 NCRMS summary between 2010 to 2017

Year	Number of rural residents covered (million)	Coverage rate of NCRMS (%)	Average Premium per capita (YUAN)	Number of rural residents reimbursed (million)
2010	836	96.00	156.57	1087
2013	802	98.70	370.59	1942
2014	736	98.90	410.89	1652
2015	670	98.80	490.30	1653
2016	275	99.36	559.00	657
2017	133	100	613.46	252

Resource: China health and family planning statistics yearbook 2018
Exchange rate: 1CAD=5.2 YUAN

The decreasing number of rural residents being covered by NCRMS was caused by the conversion from NCRMS to URSMI as well as rapid urbanization in recent years. The NCRMS insurance scheme covered inpatient and catastrophic outpatient expenses, with further outpatient expenses covered depending on the region (W. C. Yip et al., 2012). Thus, the gaps in healthcare coverage in rural areas have declined and extensive healthcare insurance coverage of uninsured rural residents was seen as the largest achievements of health reform in the rural sector. However, the chief characteristic of NRCM is "Low level and wide coverage"; challenges remain in terms of unaffordable healthcare services and quality of care in rural areas.

Unaffordable healthcare services are a major social problem in rural China, especially as a cause of illness-related poverty. In the context of age-old distortions of healthcare service prices, the healthcare providers' incomes relied on "markups" of inappropriate overprescribing, health devices, consumable health materials and laboratory tests, etc. This is done in response to revenue lost caused by governments caps on medical service prices - a 15% profit gain for drugs and 10% for medical devices (C. M. Yip, Hsiao, Meng, Chen, & Sun, 2010). As time passes, such institutional weakness and environment seems rational and acceptable to balance the conflicts of interest among variable healthcare stakeholders. But these practices pose serious risks for patients. A study in Shaanxi province found that the household burden of chronic diseases was associated with healthcare payment-induced poverty. Furthermore, the likelihood of poverty caused by chronic diseases was higher in rural areas than in urban areas (Lan et al., 2018). In contrast to other developing countries, China is unique in high use of injections. At least three out of ten patients were prescribed injections, two to three times the WHO standard (Y. Li, Xu, Wang, Wang, & Lu, 2012).

Consequently, healthcare providers were financially incentivized to overuse more expensive and profitable services, medicines, health materials and laboratory tests. This led to high costs, inefficiencies, poor quality, and weak medical ethics (H. Wang et al., 2011; C. M. Yip et al., 2010). One study found that 30% of rural patients in China were prescribed infusions (8 bottles/person/year) in 2013, which is two to three times higher than the World Health Organization (WHO) standards (2.5-3.3 bottles/person/year) (Y. Li et al., 2012). In 2012, medications costs accounted for 54.9% and 48.2% of per capita outpatient and inpatient costs in township health centers of the rural healthcare system (CNHDRC, 2015).

Beyond the unaffordable healthcare services, another key issue with the healthcare system in rural China is the lack of effective monitoring of the usage of medicine and medical devices. As a result, there are concerns that inappropriate behaviors by providers is not only fueling medical expenditures, but also affecting medical quality and patient safety. The problems are compounded by the limited clinical guidelines in the rural healthcare system and buy the low incomes of rural healthcare facilities that are heavily reliant on this markup. For example, another article found that Computerized tomography (CT) scanners and Magnetic resonance imaging (MRI) machines were being over-used in rural regions, which was resulting in high healthcare expenditures and unnecessary exposure of patients to radiology (T. Liu & Jin, 2009). It is arguable that such misuse of resources may be at least partly due to the absence of practical guidelines and effective monitoring mechanisms. While the over use of medical services has attracted wide attention, shortages of medical services in rural areas of China cannot be ignored. For example, in diagnosis of COPD, the lung function test is compulsory, but most of the China rural healthcare

institutions cannot offer such services to support appropriate and accurate COPD diagnosis.

Both of these problems can be traced to irregular behavior of physicians, imperfect management and irrational oversight measurements. There is a popular sentiment to adopt CP to improve care quality and health outcomes at a relatively low cost.

1.3. Healthcare reform

The Chinese healthcare system has gone through several phases of reform:1) between 1949 and the late 1980s, healthcare reforms were focused on equality due to the planned economy. The Chinese government created a health system gradually, in a fashion similar to other communist states. In this period, the government owned and operated all community healthcare facilities and employed the community healthcare workforce (so-called “barefoot doctors”) to provide services for free. At that time, the Chinese rural health system was recognized by WHO as a model of service in developing countries; 2) from the late 1980s until the early 2000s, along with the introduction of market forces in all economic and social sectors, government scaled back its inputs to the health sector and exerted little control over the behavior of health care organizations. This change resulted in a vast majority of uninsured patients. Healthcare workers acted like private entrepreneurs. In response to a rapid growth in health expenditures and discontent with healthcare, the government introduced the NRCMS to mitigate the financial burdens of disease among rural residents. And 3) from the late 2000s, in response to rapid growth of healthcare expenditures, healthcare reforms attempted to balance equality and efficiency with the quality of care and reasonable costs (H. Wang et al., 2011).

Since 2009, the national government officially abandoned experimenting with a healthcare system based predominantly on market principles and initiated a major new phase of healthcare reform that aimed to provide an affordable, equitable and accessible national health system to the public by 2020 (Reynolds & Mckee, 2012).In the new round of national comprehensive healthcare reform launched in 2009, and continuing through 2012, the government committed 850 billion YUAN. (The equivalent of 163.5 billion CAD, at an exchange rate of 5.2 YUAN = 1CAD.) Five main independent parts were included in the reforms: 1) expanding health insurance coverage (with co-payments) to most of the population; 2) establishing a national essential medicine system; 3) strengthening the delivery system of basic public health services; 4) improving the primary healthcare operating system; and 5) conducting trials of public hospital reform (NHC, 2009). Out of five major reform parts, public hospital reform was recognized as the hardest part. Progress has been slower than the other four reform fields, since the change of behavior and interests of clinical practitioners from policy initiation to frontline practice is a complex and slower working mechanism. Within rural healthcare, this problem is bigger, more complex and more severe, given the county hospitals in a leading role, underpinned by the township health centers and village clinics. Because of low patient trust in village clinics and township health centers and the absence of effective management approaches in patient flow, the county-level hospitals in rural China are always overcrowded and excessively general in provision of treatments as patients often seek care at county-level hospitals for simple health problems. Although most Chinese counties have initiated tiered reimbursement systems, with higher reimbursement for care at village clinics and township healthcare centers, many patients continue to use county-level hospitals for minor conditions, NCD conditions, and rehabilitations. A

referral system is typically not in place(Barber et al., 2014). Therefore, the county-level hospital is criticized as an important driver of increased healthcare costs and limited public access to qualified and standardized medical services. Meanwhile, faced with conflicting interests from variable governing stakeholders, county-level hospital reform remains one of the least understood areas of healthcare reform and progress has been slower than the other four reform fields described above. Thus, county-level hospital reform received the concern and attention of policy makers and was targeted as a key part to advance future healthcare reform plans. In 2012, the State Council issued the "Opinion on comprehensively Carrying Out County-Level Public Hospital Reform and The Instructions on Urban Public Hospital Comprehensive Reform's Pilot Work." This proposed to improve the quality of treatment through CP and electronic medical records, eliminate completely the bonus rewarded for over-prescription and standardize evidence-based clinical practice.

The evolving rural health service system and associated health insurance schemes are helping to address the problem of accessibility and unaffordable care. Following the launch of the 2009 healthcare system reform, a three-tier rural healthcare delivery system composed of county-level hospitals, township health centers and village clinics was strengthened distinctly in most areas, and these institutions worked in coordination to meet the healthcare needs of local rural residents. These governance reforms for healthcare delivery and financing have made a significant difference in solving the problems of past services. For example, the accessibility changes in healthcare services for urban and rural residents can be summarized as Table 1-5.

Table 1-5 Accessibility changes of healthcare services for urban and rural residents

Year	Visit rate within two weeks (%)		Admission rate (%)		Neonatal delivery rate in hospitals (%)	
	Rural residents	Urban Residents	Rural residents	Urban residents	Rural residents	Urban residents
2003	13.9	11.8	3.4	4.2	62	92.6
2011	15.3	13.7	8.4	10.1	95.9	95.5

Resource: Reports of the China's health reform progress, 2013, NHC

In terms of access to healthcare, reforms aimed to expand insurance coverage, and change reimbursement rates and government subsidies. By 2020, 97.5% of the rural population will be covered by the NRCMS (Cheng, 2013) and a package of free basic public health services will also be provided to reduce inequality. Although the expansion of health insurance has made medical services more affordable, challenges remain relating to inappropriate provider behavior increasing medical costs and reducing the quality of care.

Two approaches to reform have previously been reported: eliminating the mark-up alone and eliminating the mark-up alongside wider hospital reforms:

- A review of hospitals in Zhejiang province showed that by cancelling markups and increasing service prices, drug spending per outpatient visit decreased by 8.2% and drug spending per inpatient visit decreased by 15.4%, while service expenditures per visit increased by 23.0% for outpatients and 27.7% for inpatients (H. Zhang et al., 2015).
- The integrated approach, known as the Sanming Model, after a city in Fujian province in southeast China (Fu, Li, Li, Yang, & Hsiao, 2017), involved not only addressing payment systems, but also restructuring the hospital governance structure and realigning physician incentives. This model was

shown to reduce drug expenditures for inpatients and outpatients (Fu et al., 2017).

Despite these reforms, overtreatment due to perverse financial incentives for providers as well as inadequate access to treatment for patients remain major issues in rural areas and are the focus of ongoing healthcare reforms. Interventions that can simultaneously address these issues and show measurable impacts on patient and provider-relevant outcomes should be investigated.

Part two: overview of stroke and CP, and CP for cerebral infarction

1.4. Stroke and cerebral infarction

1.4.1. Clinical characteristics of stroke

Stroke occurs when blood flow to the brain is restricted, causing the death of brain cells (Association, 2016). The impact depends on both the location and severity of the damage. The most important risk factors for stroke are high blood pressure, heart disease, diabetes, smoking and prior stroke (Prevention, 2019).

Stroke can be categorized into two types: ischemic, which is caused by a lack of blood flow and accounts for 60-80% of strokes, and hemorrhagic, which is caused by bleeding (Health, 2019; Matthias et al., 2003; Yunhua et al., 2015). Ischemic strokes are further divided into thrombotic and embolic. In thrombotic stroke, a blood clot forms in an artery supplying blood to the brain. In embolic stroke, an embolism (blood clot or other material) travels through the bloodstream to an artery in the brain. CI is a major type of ischemic stroke resulting from a blockage in the blood vessels that supply blood to the brain (WIKIPEDIA, 2019a). A Chinese national surveillance program using CT scan results shows that on average, CI accounts for 62.4% of total stroke cases, ranging from 43% to 79% among patients with CT scan rate greater than

75% across ten cities (Wu et al., 2013; L.-F. Zhang et al., 2003). Thus, it was concluded that CI was the dominant subtype of stroke in Chinese populations. The frequency and proportion of CI is higher for people over 45 years old than younger people, but there is no significant difference between men or women (L.-F. Zhang et al., 2003).

Treatment generally focuses on early intervention followed by rehabilitation. The 2018 guidelines from the American Heart Association/American Stroke Association detail the first two weeks of care and cover 1) pre-hospital management, 2) urgent and emergency evaluation and treatment with intravenous and intra-arterial therapies, and 3) in-hospital management, including prevention and treatment of complications(Powers et al., 2018). The guidelines emphasis the integration of pre-hospital and in-hospital settings.

1.4.2. Burden of disease (clinical burden and economic burden)

Stroke is the second leading cause of death globally, leading to more than 5 million deaths per year, 11.1% of total deaths worldwide (Donkor, 2018; Lancet, 2018).

Stroke has a significant impact on the health of patients and caregivers (Meng et al., 2012). Patients perceive that their physical function worsens over time, although they may be able to adapt and maintain a good quality of life. Caregivers' health is also affected, particularly in terms of mental and emotional aspects of quality of life. On average, 0.27% of gross domestic product (GDP) was spent on stroke by national health systems, and stroke care, equivalent to around 3% of total healthcare expenditure (Evers et al., 2004).

In China, age-standardized stroke prevalence and mortality rates were 1,114.8 per 100,000 people and 114.8 per 100,000 person-years, respectively, in 2013 (W.

Wang et al., 2017). Stroke is the leading cause of years of life lost (YLL) and disability-adjusted life years (DALYs). There are geographical differences in stroke incidence in China: the Northeast has the highest incidence (486 per 100,000 person-years), whereas the incidence rate is significantly lower (136 per 100,000 person-years) in Southern China (Gao et al.; Liping, David, Wong, & Yongjun, 2011).Furthermore, the same study found that the burden of Stroke in terms of YLLs and DALYs was higher in rural areas compared to urban areas.

In 2003, national direct medical costs were 23.732 billion YUAN for ischemic stroke and 13.72 billion YUAN for intracerebral hemorrhage (Y. L. Wang et al., 2007). Together stroke is the most costly disease in terms of medical expenditure in China and growth of spending on stroke exceeded the rate of GDP growth from 1993 to 2003. In 2014, there were 1,705,459 CI patients who were discharged from hospitals (922, 992 from county-level hospitals) with an average LOS of 11.7 days (10.8 days for county-level hospitals) (Commission, 2015). In 2014, the average fee for CI hospitalization at county-level health institution was 8,841.4 RMB, accounting for 83.8% of annual income of rural residents (Commission, 2015).

Current levels of screening, prevention, treatment and rehabilitation are far from adequate in China. Research undertaken by the China National Health Development Research Center (CNHDRC) found that total hospitalization costs were particularly high with respect to stroke among some county-level hospitals. Also, patients who might be best managed in a community setting (i.e. a village health center), were being admitted unnecessarily to county level hospitals. These findings for stroke are in line with the general themes of overtreatment and under-use of community care in China, as outlined earlier in the chapter.

The stroke care pathway in China is not well integrated, which prevents patients from accessing comprehensive care (Z. Li, Jiang, Li, Xian, & Wang, 2019). This results in longer pre-hospital delay, low intravenous tissue-type plasminogen activator (tPA) use, poor adherence to medicines and low use of rehabilitation services (Bettger et al., 2017; Jiang et al., 2017; Zixiao Li et al., 2016). The lack of linkage across settings has also limited the ability to assess the outcomes and quality of stroke care in China (Z. Li et al., 2019).

Consequently, there is an urgent need to explore and establish efficient integration systems for screening and prevention: stroke networks to disseminate health knowledge, advocate healthy lifestyles, conduct screening for people at high risk, undergo early diagnosis and intervention, focus on and strengthen primary prevention and secondary prevention, and improve the current situation with respect to treatment and rehabilitation.

1.5. Clinical pathways

CP, also known as “care pathways” “critical pathways” “care maps” or “integrated care pathways” are defined as patient-centered schedules of medical and nursing procedures, including assessment details for therapy and consultations designed to reduce variation in clinical practice, optimize patient outcomes, minimize resource utilization, maximize the clinical effectiveness of process of care, accommodate communication between patient and healthcare professionals and improve the quality of documentation (J. Kwan & Sandercock, 2002; Rotter et al., 2011; K. Vanhaecht, De Witte, Depreitere, & Sermeus, 2006).The characteristics of CP can be summarized as evidence-based, organized, goal-defined and time-managed (by hour for emergency care, by day for hospitalization or by visit for homecare), with interdisciplinary coordination and improved documentation coupled with payment

reform. While clinical guidelines and protocols can provide generic recommendations for specific conditions or interventions, CP outlines the best operational process for care within the local structure and supporting systems (K. Vanhaecht et al., 2006).Thus, CP is a tool which translates the best available evidence and guidelines into multidisciplinary plans of best practice for people with particular conditions (CLINICAL, 2013). In addition, CP is a valuable tool for focusing on quality and coordination of care, It can apply to multi-disciplinary teams and cover interventions for prevention, treatment and rehabilitation (CLINICAL, 2013). In practice, CP is developed in a particular setting to define the steps to be taken within the local structure, systems and time-frames. Sometimes, the healthcare service providers are required to follow and evidence CP steps in order to be reimbursed for delivery of patient care.

CP was originally used to deal with medical errors and unnecessary variation observed in term of patient care and outcomes for certain conditions, as well as fast-growing healthcare costs. CP reduced prolonged length hospitalization and unnecessary admissions (Crummer & Carter, 1993; Weingarten, 2001).The concept of CP was derived from industry practice and introduced to the health sector for the first time at the New England Medical Center (Boston, United States) in 1985, in response to inappropriate behavior including an escalating volume of care delivered and little focus on quality (Wikipedia, 2019b). In that scenario, the high volume and inappropriate variations in care contributed to inefficiency and resulted in inappropriate expenditures for labor, medication, laboratory procedures, supply chain redundancies and inefficient communication (Hipp, Abel, & Weber, 2016). Specifically, when variations of prescriptions are based on preference or interest rather than evidence-based decision making, the healthcare service provided will

increase risks to patient safety and lower the increase inefficiency in the utilization of healthcare funds (Hipp et al., 2016). Initially, early CP concentrated on simple conditions or surgical procedures, whose care had less variation in pathology and mature treatment in practice. They were easier to standardize in according with existing references and were shown to improve health outcomes and efficiency while reducing costs and variability (Crummer & Carter, 1993). Later, CP began to be used to manage complex or chronic conditions such as stroke, diabetes, cancers, and palliative care. As an instrument to improve clinical processes, CP is being implemented across individual hospitals and healthcare systems in the USA, Australia, the UK and Singapore (Cheah, 2000).Over the past few decades, CP was increasingly used to decrease LOS and reduce unnecessary costs while maintaining or improving quality of care (K Vanhaecht et al., 2012).Some international studies have shown that the application of CP appears to shorten the length of hospitalization stays, lower mortality rates and in-hospital comorbidities, and all while maintaining quality of care, improving patient outcomes, interdisciplinary cooperation and staff satisfaction (Hanna et al., 1999; Isozaki & Fahndrick, 1998; Jacavone, Daniels, & Tyner, 1999; Mabrey, Toohey, Armstrong, Lavery, & Wammack, 1997; Maxey, 1997).Therefore, CP, informed by evidence of best practice, has been recognized as an effective tool for enhancing individual health outcomes and reducing utilization of overall health resources. Consequently, CP may reduce medical service costs and improve the cost effectiveness of healthcare delivery, coping with changes in payment mechanism (Rotter et al., 2011; Y, 2012). A systematic review of CP working on stroke was conducted following routine approach, more details can be found in chapter 2.

1.6. Clinical pathway for cerebral infarction

As proposed in the Helsingborg Declaration and by the American Heart Association, access to well-organized multidisciplinary care is recognized as one of the most effective treatment for CI patients (J. Kwan & Sandercock, 2002). However, variations in the organization and delivery of healthcare reduces the efficiency of recommended treatment. The CP can facilitate the process of general medical and nursing care, as well as coordinate and guide in an effective way the standardized collaboration of multidisciplinary professionals (J Kwan, 2007; Silke et al., 2012).

In the acute-care hospitalization setting, CP is usually initiated at the time of admission and terminated when the patients are discharged or transferred to another setting (J Kwan, 2007; Silke et al., 2012). Within the acute stage, accessibility of timely and appropriate assessment, therapy, and early-stage rehabilitation are crucial for effective management of patients admitted to the hospital with acute CI; this kind of care can best be achieved through a coordinated and integrated approach across the healthcare continuum (Fagerberg, Claesson, Gosmanhedström, & Blomstrand, 2000). For example, in the hyper-acute phase of CI, an Emergency Clinical Pathway (ECP) can facilitate the decision to provide intravenous thrombolysis for eligible patients. In the first few days after admission, a CP can also ensure that all the important processes of care are provided, such as fever management, glucose monitoring and swallowing screening. In the stage of inpatient rehabilitation, the CP can then coordinate interdisciplinary communication between the physicians and nurses of the stroke unit and ensure a smooth discharge with clear instructions for follow-up (J Kwan, 2007). Additionally, a well-designed CP should take many factors into consideration during treatment, such as unpredictable courses of illness including the occurrence of complications and co-morbidities such as diabetes, hypertension,

infections, dehydration, incontinence, depression and dysphagia, etc. (David, Anne, Inigo, & Lalit, 2002; Martínez-Sánchez et al., 2010). In order to accommodate such challenges, "co-pathways" were designed to deal with the common co-morbidities or complications of CI in a more structured and organized manner. These can be shared across departments within the same health institution (Dykes, 1997; D. Sulch, ., I. Perez, ., A. Melbourn, ., & L. Kalra, . 2000). This setup should ensure that appropriate care is offered to treat the patient conditions at the right time.

Part three: Overview of CP Intervention in pilot hospital and study objectives

1.7. Intervention overview

1.7.1. Rationale of intervention in the setting of rural China

Within the China healthcare reform strategy, public hospital reform is recognized as the hardest job in balancing the conflict of interests between various stakeholders. As the major provider of medical services in Chinese healthcare system, there is evidence that hospital healthcare providers have been financially incentivized to over- or under-provide healthcare services, and concerns remain that inappropriate behaviors by providers are fueling costs and affecting quality of care and patient safety. With it is large patient population and prolonged institutional weaknesses, the rural healthcare system was seen as the most complex and difficult sector in which to process changes in disease management. Due to weak disease management capacities in grassroots health institutes (township healthcare centers and village clinics) and the absence of effective management approaches to patient flow, large numbers of rural patients often seek care at county-level hospitals, which leads to overcrowding in those hospitals. The overcrowding and extensive use of treatments motivated by profit-seeking rather than healthcare was criticized as an important driver of increased

healthcare costs and for settling up barriers to the access of quality medical services by the public Because of this, the reforms of county-level hospitals received great public attention and was seen as a sign of healthcare reform success. Moreover, the State Council issued the "Opinions on Comprehensively Out County-level Public Hospital Reform Pilot Work" in 2012, which proposed to improve the quality of treatment through CP and encourage the exploration of different and innovative local models.

The institutional weakness may at least be partly due to the absence of practical CP and effective monitoring mechanisms for the use of medicine and medical devices. Following the raising awareness of evidence-based medicine and the application of same decision-making in hospital management and clinical practice has evolved from being option-based to being based on sound scientific procedure (Rotter et al., 2011). This change provides the conditions and opportunities to introduce CP into rural public hospitals to strengthen the system and bring changes in behavior. Therefore, evidence-based CP not only has been introduced as a realistic option for optimizing diagnosis and treatment techniques for public hospitals, but also to provide sound scientific evidence for making policy decisions.

Development of evidence-informed CP interventions has raised the interest of health authorities and rural medical institutions as a potential way to reduce variation in clinical processes and to help contain fast-growing medical costs while improving the quality of care. Trials of CP in rural pilot areas can provide real world evidence to help rural healthcare reforms take the next step. As the leading actor in the rural healthcare system, county-level hospitals were chosen as pilot sites because the county-level government has been given the authority as part of national health reform to create and define reform trials. By empowering local governments, project

interventions are more efficient and the potential risks posed by unexpected confounding factors, as well as outright failures, can be recognized and contained more quickly. In other words, if the reform trial within the county scale is not successful, the negative impact or intervention or risk factors can be controlled in scope. Conversely, successful experiences can be recognized by upper-level health authorities, and the pilot trial can be extended on a broader scale to benefit more people. This is also the usual method to push forward reform, given that China is a diverse country. This approach is described proverbially as “crossing the river by the feel of the stones”.

1.7.2. The overview of intervention

Resulting from extensive consultation and investigation with peers from the international community , the think tank of Chinese National Health Authority(NHC), China National Health Development Research Center (CNHDRC), in collaboration with the National Institute for Health and Care Excellence (NICE) International embarked on a pilot project to develop and implement evidence-informed CP for two high priority disease areas, chronic obstructive pulmonary disease (COPD) and stroke. The intervention was designed as a comprehensive reform in which CP is combined with other reforms, including capacity training sessions for clinical practitioners, management and development of data management systems, and incentive management approaches (not designed as a stand-alone pilot project.) The implementation of a CP with other supporting systems for selected conditions took place in four counties, representing of various levels of development in China, Figure 1-1.

Figure 1-1 Location of pilot sites in China

The target counties were chosen based on predefined criteria: 1) strong willingness and enthusiasm to actively participate; 2) sound project management experience; 3) better support of information systems in county hospitals; 4) reflection of a diversity of economic conditions useful in dissemination and reproduction; and 5) minimization of potential confounding factors such as other, simultaneous reform trials which could interfere with assessments of this trial. Four candidate areas were selected as the pilot areas: Huangdao county of Shandong province (located in Eastern China and representative of high-income rural areas), Wen county of Henan province (located in middle China and representative of middle-income rural areas), Qianjiang county of Chongqing Municipality (located in Southwest China and representative of middle and low-income rural areas), and Hanbin county of Shaanxi province (located in Northwest China and representative of low-income rural areas).

After extensive engagement with various stakeholders (such as local practitioners, policy makers from rural health authorities and institutions, clinical consultants, senior policy makers from ministries, international counterparts, etc.), the research team outlined the intervention activities as per Figure 1-2. This divides the project activities into two major parts: preparation and implementation. Within each of the two parts, there were individual project activities designed to facilitate the development of the intervention.

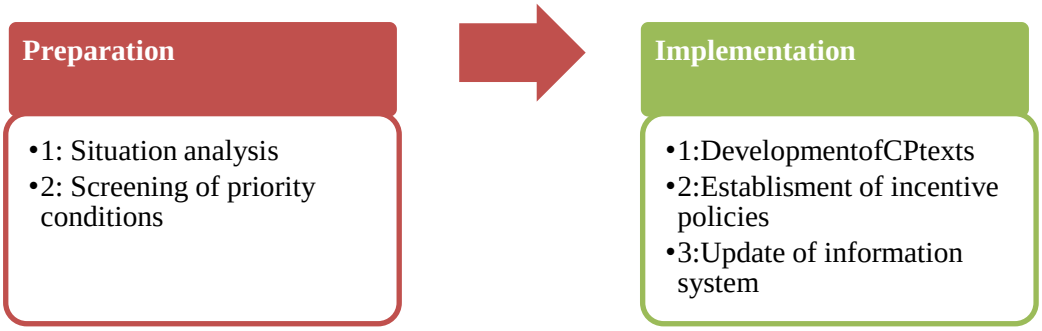

Figure 1-2 Overview of intervention activities

Preparation stage:

Target conditions were identified based on a broad-ranging situation analysis of the pilot areas, including a review of the literature, local socioeconomic and demographic information, health system indicators, analysis of the local disease spectrum, top-down analysis of the financial burden of disease, and consultation with clinical experts and local stakeholders. After comparing the burden of disease and corresponding economic burden across the four pilot areas, COPD and stroke were chosen as the target conditions for the intervention. According to local clinical demands, stroke was subdivided into three categories—cerebral hemorrhage, cerebral infarction and transient ischemic attack (TIA).

Implementation stage

To fully consider professional competencies and local settings, existing clinical practice of the study sites was used to establish the baseline for CP development. To reach a consensus, amendments to existing practices and business processes were made iteratively, incorporating principles from national guidelines and comments from senior clinical experts on COPD and stroke. As a dynamic intervention, the CP contexts were optimized continuously to respond to changes in local setting and in response to other confounding factors. This is normally done during an update or as part of a review within each project year.

There were two major components for each CP context template. One is the description of general principles and standards of procedure for treatment(Appendix A1), including, but not limited to, target conditions (diagnosis with International Classification of Diseases-10th Revision [ICD-10] code), diagnostic references, treatment options, LOS, inclusive and exclusive criteria, summary of recommended tests and medical principles of treatment, status at discharge, etc. The inclusion criteria are 1) primary diagnosis must be cerebral infarction (ICD10: I63) and 2) those patients with secondary diagnosis can be covered by the current CP if they do not need special treatment for their secondary diagnosis and if the secondary diagnosis does not have any impact on the implementation of cerebral infarction pathway. This general introduction serves as a simplified clinical guideline to outline the basic rules of standard procedure. The other component is a detailed list of daily-prescribed actions that might be taken by physicians (Appendix A2), which have been installed into hospital information systems for processing. In order to ensure the quality of service and physician adherence to the CP, the items were allocated into mandatory and optional categories according to their importance and feasibility in relation to the

condition. Specifically, mandatory items, such as blood test, urine test, myocardial enzymes, coagulation function, are applied to all patients admitted into clinical pathway management and an explanation of decisions made must be recorded for review in some extreme cases. The optional items can be ordered by physicians depending on patient needs and will vary between cases, such as skull CT, oxygen inhalation, ECG monitoring, etc.

Meanwhile, with the aim of more efficient delivery of care, an incentive mechanism was derived to motivate practitioners' participation and improve the adherence of clinical staffs. If an extra bonus payment was proposed by hospital management on the basis of quality auditing, the doctors are able to receive benefits to subsidize their inputs, rather than from a "mark-up" on medicine and testing. Meanwhile, hospital management introduced a series of supportive management measures to assist with the implementation of CP in hospitals. These included linking monthly salary with volume and quality of patient managed by CP, drafting regulations on internal supervision and specifying related management rules. In short, the design of the incentive mechanism aimed to shift the behavior of healthcare providers from "more prescriptions, more income" to "reasonable prescriptions, better income".

In order to accommodate the routing monitoring and oncoming impact evaluation, the pilot hospitals created clinical management modules within the existing general hospital information system. They embedded digital pathway templates and achieved seamless links with the original hospital information systems(CNHDRC, 2015). Finally, patient-oriented project data, especially the expenditure data, could be tracked through the electronic management module at any time. Based on the monitoring results, supported by real world data, local

stakeholders' sense of evidence-informed decision making was reinforced and encouraged access and use of evidence (CNHDRC, 2015).

Building capacity was a crucial feature of the intervention and was repeatedly stressed throughout the course of the project lifespan (CNHDRC, 2015). There are two ways of building capacity. One is training clinical practitioners about CP content. The other is training to use the clinical management module tailored for the intervention. The first training aims to acquire an understanding of evidence-based treatment among clinical practitioners. This may vary from their long-term habits and practices. Another method is training to facilitate the physician use of supportive information systems, in order to improve working efficiency and strengthen the process of behavior change. Ultimately, these two types of training not only can increase adherence to CP in physicians and ease patient management, but can also facilitate route monitoring by providing evidence-based defaults for care delivery and facilitating awareness of its impact.

Chapter 2 Systematic review of literature

Summary of Chapter

Introducing evidence-based CP is a potential solution to address practical problems described in the previous chapter: the high burden of CI; the overuse of healthcare services in China rural areas; and the poor quality of care in China's rural healthcare system. Piloting CP in a rural area may provide evidence to guide the direction of further healthcare reform in China.

However, since there is high variance in the nature of the disease and a dependence on local circumstances for treatment, the application of CP in management of in-hospital CI patients is associated with conflicting evidence. Some studies concluded that there was insufficient evidence to justify the advantages of CP implementation for acute CI management in terms of major clinical outcomes (J. Kwan & Sandercock, 2002). On the other hand, some studies stated that the CP can significantly improve the CI patients outcomes, such as 30-day mortality, LOS and hospital re-admission rates (Panella, Marchisio, Brambilla, Vanhaecht, & Di Stanislao, 2012).

This systematic review aims to investigate the effectiveness of CP among patients admitted into hospital care with diagnoses of acute CI, compared to alternative treatments in Randomized Clinical Trials (RCT).

2.1. Methods

The systematic review was conducted based on principles of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses（PRISMA）standard (Higgins & Green, 2008; Moher, 2010).

The studies were screened independently by thesis author and a second reviewer (Mr. Zhonghan Li, research fellow from CNHDRC), using pre-defined inclusion and exclusion criteria to identify appropriate publications and process full text review. The second investigator has no conflicts with the study. Any conflicts between the interpretation of the thesis author and the second reader were accommodated by discussion in first, and third party judgement was designed to deal with the disagreement, but which was not applied in this literature systematic review.

Four databases (Medline, Embase, Cochrane library and CINAHL) were searched for peer-reviewed articles according to the pre-defined "search strategies" in Appendix B1. Articles in Chinese language were not included but were used as a source for parameters in a chapter 5 to perform Markov modeling. Target peer-reviewed articles were eligible and selected based on the following criteria:

- Target population (the patients with diagnosed acute CI hospitalization with clear demographic and baseline characteristics)
- Type of intervention (CP management, summarized as a structured hospital-based multidisciplinary plan of care and an intervention utilized to detail the steps to accommodate the recommendations of guidelines, protocols or inventories of actions in local structures.)
- Type of outcomes (include LOS, number of deaths, Short form health survey with 36 items (SF-36) general score, Barthel Index of activities of daily living (BI) score, time from dispatch to hospital, etc.)
- Type of study: the titles, abstracts and keywords of studies were screened first. Full texts of selected publications were reviewed using pre-defined inclusion criteria and exclusion criteria. The PRISMA checklist was used to standardize the

reporting of this systematic review. The primary outcomes included length of hospitalization and mortality. The secondary outcomes were SF-36 health score, BI score, number of patients receiving the swallowing test and number of patients receiving the timely thrombolytic treatment. It was decided to focus this review on RCT study design because this represents among the highest levels of evidence (Medicine, 2019).

Meanwhile, the exclusion criteria were outlined as below:

- Non-English, duplicated and published papers before the year 2000;
- Study implementing non-hospital-based (hospital-to-community-based or community-based) stroke care;
- The papers omitting introduction of RCT design;
- No full text papers or papers with difficult data access;
- Papers referring to study protocols, systematic reviews or meta-analyses.

2.2. Analysis

Meta-analysis was conducted for the pre-defined primary and secondary outcomes by using Review Manager 5.3. The Mantel-Haenszel statistical test was performed for testing heterogeneity using a random effect model and a forest plot was used to interpret the synthesis of findings. We defined the amount of heterogeneity by using the I^2. An I^2 value less than 50% indicates high homogeneity, and I^2 value greater than 50% means substantial heterogeneity. The P-value lower than 5% for the Chi-square test indicates statistically significant heterogeneity.

2.3. Results

2.3.1. Study characteristics

One thousand, eight hundred and eighty-four articles were found in the target database (Medline, Cochrane Library, EMBASE, CINAHL) and nine articles were selected for this systematic analysis according to inclusion criteria. The screening process is shown in Figure 2-1. The nine included articles were conducted in both developed and developing countries. Participants were randomly assigned to intervention and control groups to receive different health interventions. Selected studies used various outcomes to assess the effectiveness of hospital-based CP management for acute CI. Although the CP management in different papers were diverse, they all have CP management principles, such as high-priority process of care[1] (PoC), evidence-based treatment protocols, emergency clinical pathway[2](ECP) procedures, etc.

No statistically significant difference on heterogeneity was found on the baseline of the demographic and clinical characteristics in the included papers. The demographic analyses included gender, age, marital status, level of education, employment status, time from onset of symptom, risk factors, and co-morbidities. The characteristics of the selected studies are summarized in Appendix B2.

[1]Process of Care (PoC) : process of care refers to an evidence based action or intervention performed during the delivery of patient care (Hoffman, 2019).
[2]Emergency clinical pathway (ECP) : The implementation of an evidence-based acute stroke care pathway for Emergency Medical System personnel, associated with continuing medical education programs (De Luca et al., 2009).

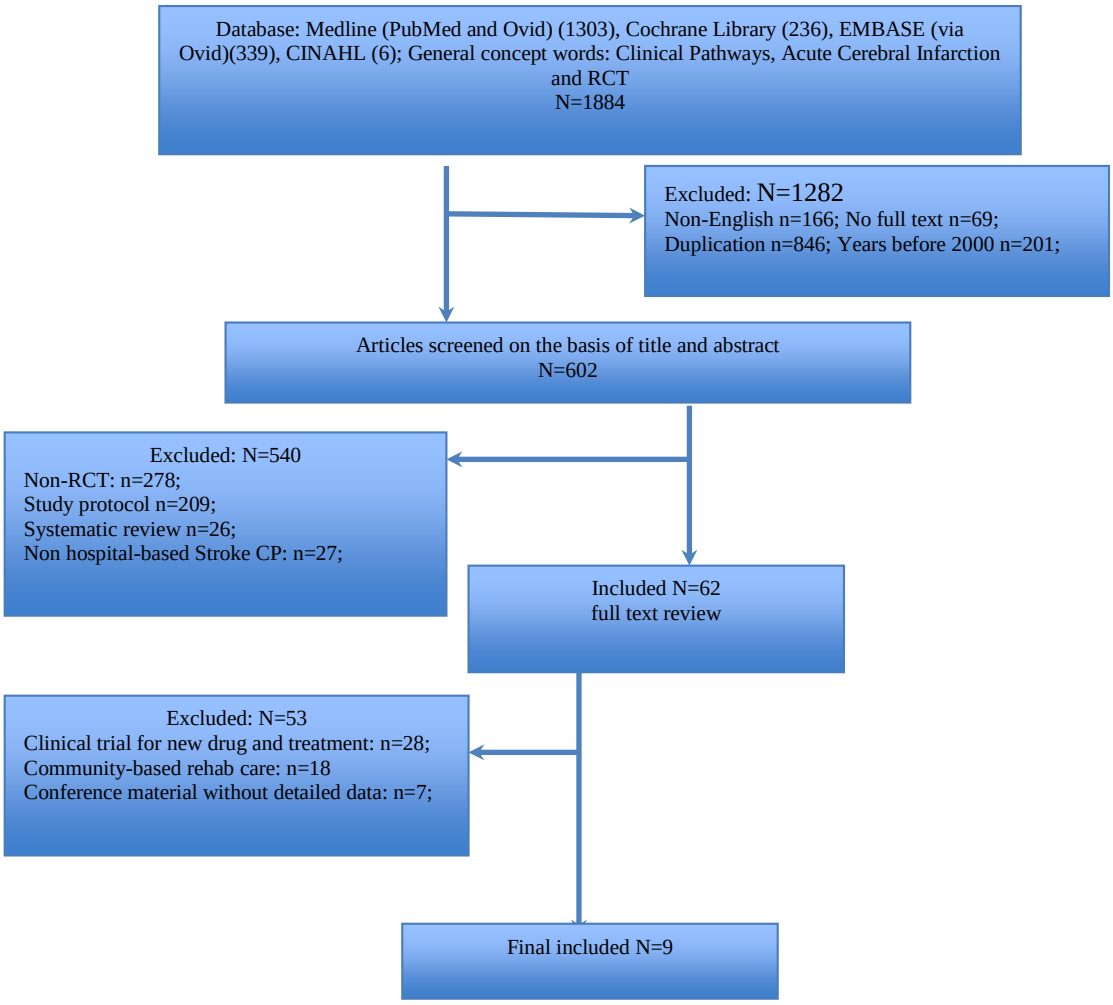

Figure 2-1 PRISMA flow chart showing study selection

2.3.2. Primary outcomes

LOS was reported as the primary outcome in the four studies. One of the studies reported LOS separately for intracerebral hemorrhage and transient ischemic attack or cerebral infarction. According to included studies outcomes, the meta-analysis showed that the average LOS in CP group is 2.02 days lower than control group though significant heterogeneity. (I^2 =91%, mean difference= -2.02, 95% CI -2.66, -1.38; p<0.00001) (Figure 2-2).

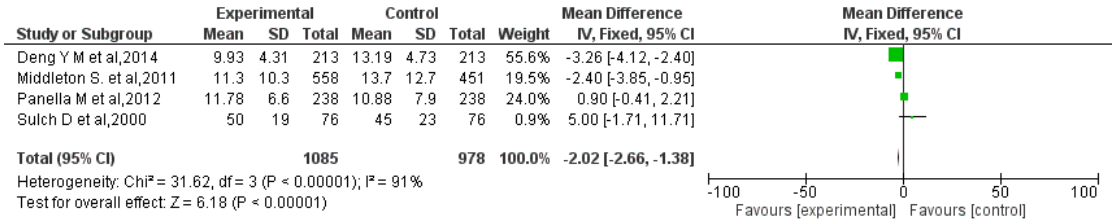

Figure 2-2 Forest plot of length of stay

Five articles reported mortality or number of death events as outcomes. Based on included studies outcome, CP favors the aggregated intervention group where the number of deaths is 0.56 times that of the control group (I^2 =25%, OR=0.56, 95% CI (0.45, 0.70), p<0.00001) (Figure 2-3).

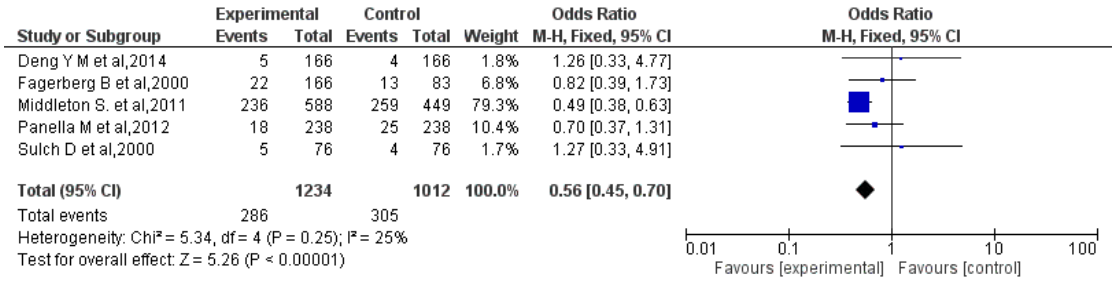

Figure 2-3 Forest plot of Mortality

2.3.3. Secondary outcome

SF-36 health score (both mental and physical components) was reported as an outcome in two studies. For the SF-36 health score, mental and physical components were analyzed separately. The general SF-36 scores in the intervention group (CP group) is 1.38 units higher than control group in the condition of significant heterogeneity (mean difference=1.38, 95% CI (0.53, 2.22), p=0.001, I^2=77%) (Figure 2-4). It was not possible to perform the Mantel-Haenszel test on the mental and physical scores separately.

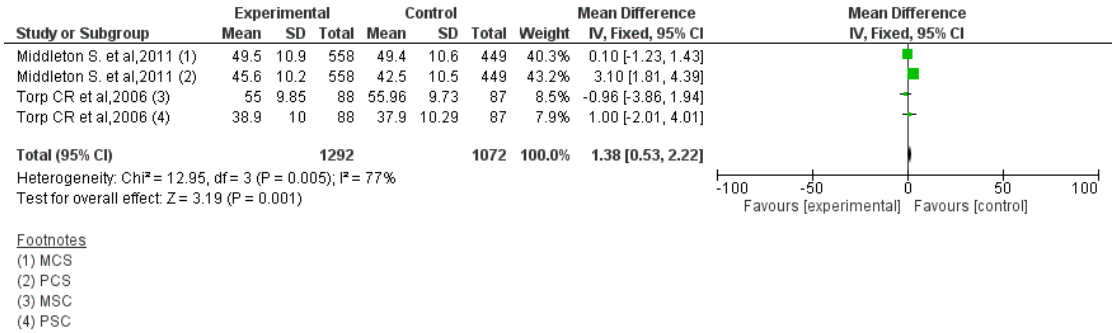

Figure 2-4 Forest plot of SF-36 score

The BI score was reported in different grades in six studies. This systematic review included the studies in which BI score 90 days after discharge was greater than 50. Analysis shows that the CP group is less likely favor the aggregated intervention group in the condition of significant heterogeneity. (OR=0.72, 95% CI (0.56, 0.93), P=0.01, I^2 =81%) (Figure 2-5).

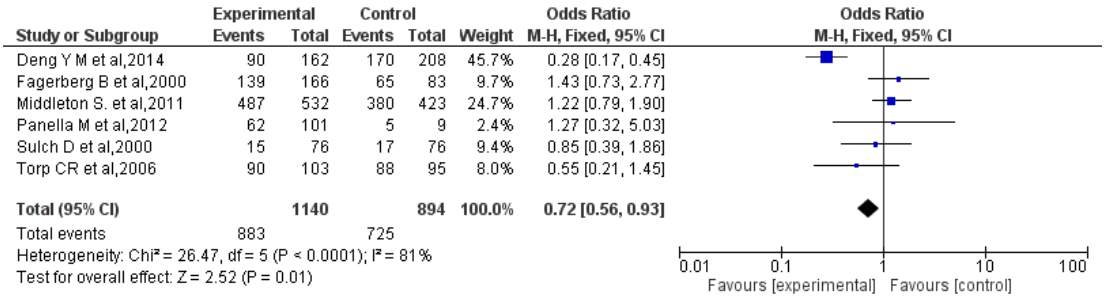

Figure 2-5 Forest plot of number of patients whose BI score greater than 50 after 90 days of discharge

2.3.4. Risk of bias assessment

All the included, randomized controlled studies were evaluated in adequacy and quality from six domains by the Cochrane Collaboration risk-of-bias tools. They are: sequence generation, allocation concealment, blinding of participants and personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and

other potential threats to validity. The article can be assessed as low risk if it meets all six criteria. Two papers (Middleton et al., 2011; D. Sulch, I. Perez, A. Melbourn, & L. Kalra, 2000) were ranked as low risk by the reviewer because they meet all six domains of assessing risk of bias. The bias assessment of each individual study is summarized in Figure 2-6 and Figure 2-7. Detailed statements about the assessment of risk of bias are shown in Appendix B3.

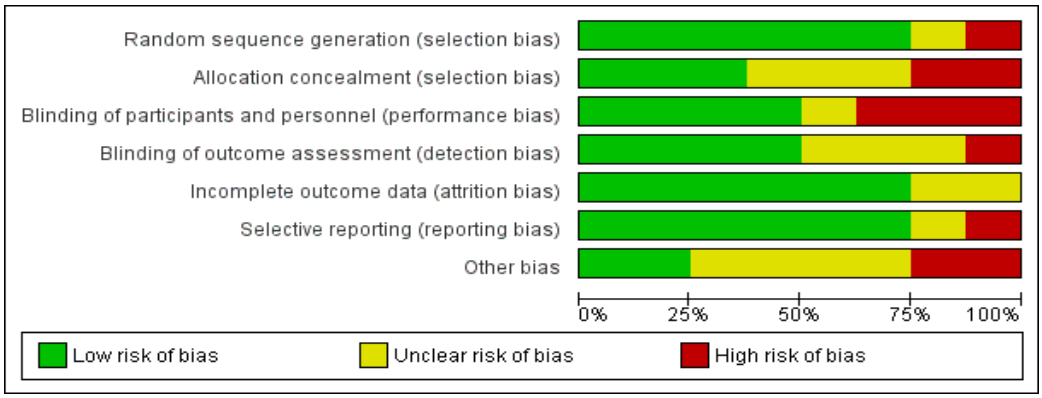

Figure 2-6 Risk of bias graph

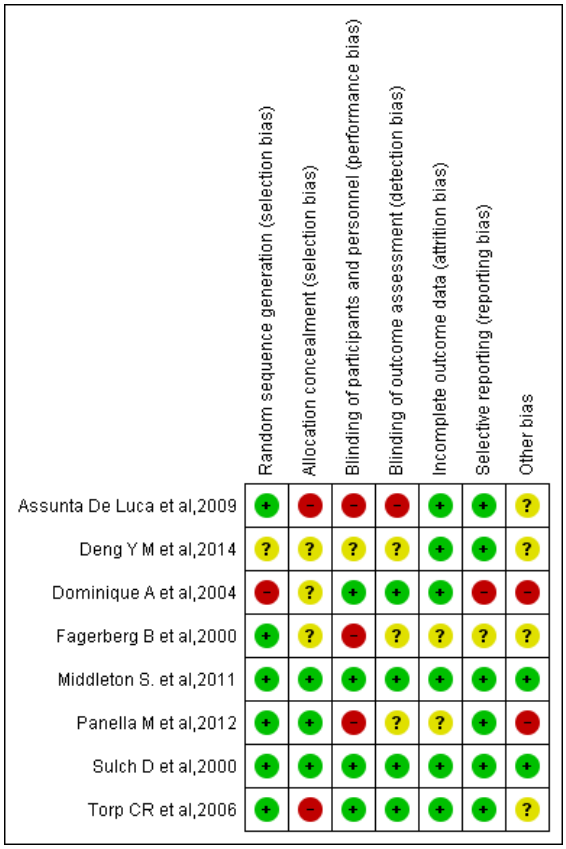

Figure 2-7 Summary of risk of bias

2.3.5. Review of cost-effectiveness studies

In order to inform the cost-effectiveness analysis, a further literature review of cost-effectiveness models relating to stroke clinical pathways was undertaken to inform its structure and inputs (see Appendix B1).

The identified six articles using MESH terms relating to cost-effectiveness of stroke clinical pathways. Of these articles, five were excluded since they did not use a cost effectiveness model. This left Wardlaw et al., which employed a decision tree approach to investigate whether computerized tomography (CT) is cost-effective in acute stroke in Scotland (Wardlaw et al., 2004).While the study did not calculate an ICER, the most cost-effective strategy was to scan all patients immediately, which cost Great Britain Pound (GBP) 9,993,676 and generated 1,982.4 QALYs across 1,000 patients.

The main limitations of the study were its geographic scope, meaning its findings may not be generalizable to other healthcare systems, and the sensitivity of the results to several assumptions such as the proportion of patients that would reach the hospital in time to be considered for thrombolysis.

2.4. Discussion

The definition of CP was not unified terminologically. However, four studies used the terms “clinical pathway” “care pathway” or “practical protocol” to describe their intervention. The interventions in individual studies were highlighted and reviewed in line with the characteristics of CP, which may appear to have differences in terms of the target condition, method of design, stages of treatment, course of illness, location of use, etc. CP management is carried out in multiple treatment stages of stroke across different departments of hospital services, such as emergency care, (emergency room [ER] /emergency medical service [EMS] /mobile stroke unit [MSU]), the stage of

hospitalization treatment (e.g. stroke unit [SU], mobile service across various specialists interdisciplinary stroke team, or conventional wards), and the stage of earlier rehabilitation (e.g. inpatient rehabilitation unit). The presence of statistical heterogeneity of selected outcomes based on eligible data limited the development of quantitative meta-analysis. However, the overall estimates of effect in the presence of such heterogeneity are still available to interpret the general correlation between the intervention and outcome changes. Although this study included nine RCT studies, there is no conclusive evidence among the studies. This makes it difficult to generate a consistent conclusion in terms of the impact of CP on health outcomes. Six studies reported positive findings in RCT in condition of limited settings; but the other three studies concluded that CP cannot generally provide additional benefits over conventional treatment. It is probable that the CP were initiated and conducted with different aims in different settings, which complicates the interpretation of the results. From the six studies with positive results for CP, two main findings can be summarized. First, CP can improve the adherence of pre-defined, high-priority PoC, and can improve mortality and trends with independence. (but the causal factors of these changes were not clarified.) (Cadilhac et al., 2004; Drury et al., 2014; Middleton et al., 2011; Panella et al., 2012; Sulch, Evans, Melbourn, & Kalra, 2002). Second, CP management is able to improve the accuracy of pre-hospital diagnosis, reduce the response time from alarm to therapy decision, and improve effective emergency treatment in acute CI settings (De Luca et al., 2009; Walter et al., 2012).However, the other three studies suggest concerns about the limitations of CP:

1) The reduction in death or institutional care was only observed in the short term, such as after three months of hospitalization. This effect did not remain after

one-year of hospitalization (Fagerberg, Claesson, Gosman-Hedstrom, et al., 2000; Sulch, Melbourn, Perez, & Kalra, 2002; D. Sulch et al., 2000).

2) In two studies, the interdisciplinary stroke team didn't show benefits in inpatient rehabilitation (Ferri et al., 2011; D. Sulch et al., 2000). CP has included standard inpatient rehabilitation care, but CP may lack the flexibility responding to the complexities of disease and diversity of patients' needs (Mahoney & Barthel, 1965; Sulch, Melbourn, et al., 2002; Torp et al., 2006). In order to maximize the effectiveness of CP in future pilot studies, there are some lessons that should be learned in dealing with the potential challenges during implementation:

1) The CP optimizes healthcare procedures, which is more likely to be effective if the basic structure of the CI service is already in place. Therefore, CP should be introduced as part of an overall quality improvement scheme rather than as a stand-alone intervention (Ringel & Hughes, 1996). Also, CP is a dynamic process. Adapted within a specific context, it should be continuously reviewed and evaluated in light of updated clinical evidence and local capacity, e.g., human resources and medical hardware infrastructure. CP is an important component of continuous quality improvement in clinical practice (Cheah, 2000).

2) CP should be strengthened in the hyperacute stage rather than stable stage, i.e. rehabilitation. Three studies found CP is less positive for inpatient rehabilitation. CI or stroke rehabilitation patients are often medically stable and managed by a coordinated multidisciplinary team within a well-structured service; hence CP is less likely to provide additional benefits. This finding also provided new evidence to support the comments derived from the Cochrane Review (J. Kwan & Sandercock, 2002), which concluded that the evidence supports the use of CP for the management of acute stroke rather than stroke rehabilitation (J. Kwan & Sandercock, 2002).In

addition, pre-hospital CP in hyperacute stroke should be emphasized and strengthened. Animal experimental and clinical evidence shows that the time to efficient treatment is the primary determinant of better health outcomes for acute CI (Jamal et al., 2013).In particular, the pre-hospital CP of acute CI management can accommodate earlier detection and treatment provided by paramedical staff, or referral to a specialist center without delay once the initial diagnosis is made.

3) CP must be flexible to accommodate clinical practice while still prioritizing patient safety. In order to successfully integrate CP into practice, there needs to be a balance between physician autonomy and prescription and evidence-based procedures. A well-defined CP includes inclusion criteria that reflect the usual care required by most of the patient population. It is significant to design exclusion criteria because of deviation from the CP due to unexpected events. For example, patient progress towards projected outcomes can be earlier or later than expected, or the patient can fail to meet project outcomes or require unplanned, additional intervention (Cheah, 2000).

4) CP is a multifaceted management tool that requires educational programs and training workshops in order to make improvement of personnel capacity and structure changes. The objective is to build consensus among different stakeholders and attain a consistent understanding of the basic terms, concepts, objectives, content, procedures, principles and variances of CP. It is also necessary for health personnel be trained in combining CP with hospital information systems. A computerized CP can issue “real time alerts” to effectively reduce medical errors. When desired, a short-term pilot study can be carried out to examine the feasibility of new CP methodologies correcting errors or omissions, improving staff competence and reducing the bias of practice (D. Sulch et al., 2000).

2.5. Conclusion

The meta-analysis done by other counterparts shows that hospital-based CP provides positive and negative results for acute CI (J Kwan, 2007; J. Kwan & Sandercock, 2002). However, this review reported a higher likelihood of positive results in relation to CP effectiveness in conditions of significant heterogeneity, when compared through randomized controlled trials with conventional medical treatments. Given the disease burden of CI and the urgent need for healthcare reform, evidence-based CP and related supporting systems can be a potential solution to lower fast-growing medical costs and improving quality of medical services in rural China. An impact evaluation should be conducted based on an evidence-informed CP pilot study to access the effectiveness and cost-effectiveness of CP in China's rural settings.

Chapter 3 Study rationale

Summary of Chapter

This chapter aims to clarify the study rationale and study objectives based on the aforementioned background and reviewing of literatures. Detailed study questions will be identified clearly as well, to facilitate the entire study.

3.1. Study rationale

There are two major reasons for conducting this study: one is related to research improvement, and the other is to practical application:

3.1.1. Address knowledge gaps in literatures

Based on the results of the systematic literature review, the use of CP in ischemic stroke management or CI remains inconclusive because of contradictory evidence. In terms of research, this evolutional study addresses at least two existing gaps in the literature on CP management for CI inpatients. The number of studies that have focused on CI in CP management is fairly small, meaning that there is little validation of the intervention's impact beyond certain subtypes of ischemic stroke. Additionally, this will be the first study to use a comprehensive and logical assessment tool to statistically describe the overall effects and estimate the cost-effectiveness of CP intervention in the setting of China's rural healthcare system. From a methodological perspective, the use of Interrupted Time Series (ITS) for this work is a practical and potentially powerful approach for evaluating the longitudinal effects of an intervention. Cost-effectiveness analysis is an increasingly used form of economic evaluation in supporting evidence-based decision-making. Analysis using Incremental Cost Effectiveness Ratio (ICER) in comparison with score-paired control group can deliver robust results and is easier to translate to stakeholders. There are few studies

conducting cost-effectiveness analysis (CEA) using the Chinese general population-based value set of European Quality of Life Scale (EQ-5D-3L). The adoption of Chinese general population-based EQ-5D-3L social value set can favor the internal validity of study efficiency and reflect the rural China setting.

3.1.2. Demonstrate real-world impact of CP intervention

The implementation of the CNHDRC CP project has received significant government interest and has been seen as a model for replication by NHC. The practical purpose of this study is to test the actual impact of CP in the rural Chinese healthcare system. It is necessary to identify the benefits and challenges of implementing CP in the pilot setting before implementation is explored in more areas. The implementation body, CNHDRC, is the policy-making think tank of the national health authority. Both the positive and potential negative implications can generate convincing evidence to inform national health policy in a timely manner and help change clinical practice, physician remuneration mechanisms and payment reforms.

Due to limited resources, this study was necessarily limited to one pilot site. However, its results may be more broadly applied to China's rural healthcare system. Additionally, the development and optimization of contextually appropriate CP will be a dynamic progress; the evaluations can assist with the continued improvement of CP implementation.

3.2. Study objectives

The general objective for this impact evaluation is underpinned by testing the overall effectiveness and cost-effectiveness of CP interventions in CI disease management using mixed methods in the setting of one selected pilot area. Based on the existing knowledge gaps, as well as the concerns of project stakeholders, the specific research objectives were formulated respectively:

1) To evaluate the CP intervention effects of CI on the pre-defined primary outcomes, in term of both clinical effectiveness and financial burden.

2) To assess the cost-effectiveness of CP compared to the usual care received by inpatients patients with CI.

3.3. Study questions

1) What is the overall effectiveness of CP in the management of inpatient CI patients in rural China?

2) Is CP cost effective, compared to usual care in the management of CI, against possible confounding factors in rural China, from a healthcare perspective, as measured by incremental cost per quality-adjusted life-year (QALY)?

3.4. Study hypothesis

It is hypothesized that in the context of healthcare system in rural China:

- CI inpatients managed by CP have better health outcomes than inpatients receiving usual treatment;
- CP intervention is cost-effective in comparison with a conventionally-treated, matched patient cohort.

Chapter 4 Methodology

Summary of chapter

In this chapter, the analytical approaches will be introduced and demonstrated. Meanwhile, the data resources, primary outcomes and analytical plan also will be presented. Three statistical approaches were adopted to undertake the data analysis: difference in difference (DID) after propensity score matching (PSM); interrupted time series (ITS); and Markov model of the short and long term cost-effectiveness of the CP intervention. DID is commonly applied by using observational data to estimate the absolute intervention change using pre-defined primary outcomes, and PSM can balance the variation of patients' characteristics using matching skills. ITS is an intuitive, practical and powerful analytical approach which is used here for evaluating longitudinal effectiveness of a time-dependent intervention before and after a specific time point using routinely collected data. Markov model is a commonly used technique to evaluate cost-effectiveness, which is able to simulate the disease trajectory and compare the relative costs and outcomes of alternative interventions (CP and non-CP).

4.1. Grouping of patients

In order to estimate the impact of the CP on the costs and outcomes of CI care, four comparison groups were created initially as depicted in Figure 4-1. "Before/ treatment" refers to the group of patients before introduction of the CP who supposed to be eligible for the CP; "Before/ control" refers to the group of patients before introduction of the CP who would not supposed to be eligible for the CP, "After/ treatment" refers to the group of patients after introduction of the CP who followed the CP; and "After/ control" refers to the group of patients after introduction of the CP who did not meet the inclusion criteria of CP.

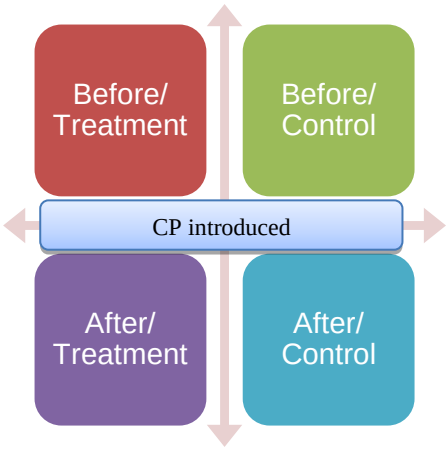

Figure 4-1 Grouping of patients

Patients were classified into the groups as follows:

- After the intervention, patients were assigned to treatment and control groups based on inclusion criteria defined in developing CP and agreed by senior stroke professionals and local stroke practitioner together.
- Before the intervention, neurology physicians of the pilot hospital performed a retrospective review of medical records to assign patients to treatment and control groups based on the inclusion criteria of clinical pathway. Actually, this process can be seen as a simulation progress to adopt the CP criterial among patients before introducing intervention.

4.2. Primary outcomes

The following measures of resource use and health outcomes were collected for patients managed by the CP or conventional treatment:

- Healthcare resource use: LOS as defined as the number of inpatient days in hospital following admission for hospitalization;

- Healthcare costs: Total hospitalization expenses and major components (medication expenses, radiology expenses, laboratory test expenses, consultation expenses and diagnostic expenses);
- Health-related quality of life (HRQoL): EQ-5D-3Lbased utility value.

Based on the rounds of discussions with stakeholders and the availability of data, only the following data were extracted from hospital information system to meet the analytical requirements, which are: gender, age, type of insurance, inpatient ID, diagnosis of discharge, ICD-10 code of discharge diagnosis, discharge status, admission date, discharge date, LOS, comorbidity information, accessibility of CT, MRI or color doppler services, total hospitalization expenses, medication expenses, radiology expenses, laboratory test expenses, consultation expenses, diagnostic expenses, admittance of CP treatment, etc.

As defined as direct healthcare expenses, the total hospitalization expenses include all the corresponding expenses of services and medicines provided by the hospital during the patients' stay. Total hospitalization expenses can be broken down to the following components: medication expenses, radiology expenses, laboratory test expenses, consultation expenses and diagnostic expenses.

Medication expenses include the expenses of medicines in relation to thrombolytic therapy, such as urokinase, antiplatelet agents, anti-atherosclerotic drugs, and free radical scavenger, drugs for improving cerebral perfusion, supportive treatment, and dilatation drug.

Radiology expenses include the expenses of imaging services, such as skull CT, skull MRI, chest x-ray, CT angiography, abdominal ultrasonography, magnetic resonance angiography (MRA), and carotid ultrasonography.

Laboratory test expenses include the expenses of biochemical examination of blood, urine, stool, liver function, renal function, electrolyte, blood glucose, blood lipid, myocardial enzymes, coagulation function, homocysteine(HCY), blood gas analysis, and infectious disease screening (AIDS, syphilis, hepatitis B or C).

Consultation expenses include the personnel charge for clinicians' routine consultation and nursing care, such as nursing assessment on admission, instruction on diets, measuring blood, pressure, temperatures and pulse. In addition, the expenses of medical consumables, such as injection syringes and gauze, were included.

Diagnostic expenses include the use of common medical monitoring equipment in relation to oxygen inhalation, Electrocardiography (ECG) monitoring, blood pressure monitoring and sputum suction, etc.

EQ-5D-3L based utility value: along the process of preparation before official intervention kick-off, the EQ-5D-3L data of hospitalized patients admitted with cerebral infarction was collected from Jun 2013 to accommodate DID, ITS and cost-effectiveness analysis. Data of EQ-5D-3L was being collected at time point of discharge for CP and non-CP patients. The trained nurses explain and accommodate the survey in face-to-face interviews. The Chinese EQ-5D-3L value set (G. G. Liu, Wu, Li, Chen, & Nan, 2014) was applied to calculate the utility value scores. More details can be found in section 4.3.3

LOS here means the hospitalization days of CI patients receiving treatment in hospitals. The LOS has been estimated with difference of admission date and discharge date. This indicator can be seen as the utilization efficiency of health services.

4.3. Data resource and process

RCT design is rarely possible to assess the impact of policy changes. Time series designs have been argued to be the strongest, quasi-experimental design to estimate intervention effects in non-randomized settings (Wagner, Soumerai, Zhang, & Ross-Degnan, 2002).

Data for this study was drawn from the CNHDRC CP Project for two targeted diseases. The project covered four representative pilot county-level areas across western, middle and eastern China. This study focuses on a detailed analysis of the data in one county, Hanbin county in Shaanxi province, western China. The selection reasons are as follows:

- It was the first pilot county to initiate the CP intervention, and therefore had the largest dataset available;
- Local practitioners had a strong interest in understanding the impact of intervention.
- A workable hospital information system was available to accommodate high-quality data collection.

Hanbin General hospital, as one of the few hospitals in the county qualified to receive stroke patients, acted as the implementation agency under the direction of the local government.

4.3.1. Data collection

Study time period: 1st June 2013 to 31st May 2017, which represents one year before and three years after the implementation of the CP on 1st June 2014.

The choice of study period was based on criteria for ITS design, which recommends that there should be at least 10 pre-intervention and 10 post-intervention

data points (Fretheim & Tomic, 2015). This provides at least 80% power to detect a change when the autocorrelation between variables is about 2 (Ramsay, Matowe, Grilli, Grimshaw, & Thomas, 2003).

Sample size: Inpatients admitted to Hanbin General Hospital who were diagnosed with CI were included in the study. CI was defined by ICD-10 codes I63.901 (multiple cerebral infarction), I63.902 (cerebral infarction), I63.903 (lacunar infarction), and I63.301 (sequelae of cerebral infarction) (Walter et al., 2012).

Sample size considerations were based on the number of observations and time points at which data would be collected. As a pilot observational study, the selection of study sites and overall sample size were partly driven by pragmatic considerations. The sample size in ITS analysis depends on the number of CI hospitalized patients treated at the pilot hospital in Hanbin over the four-year period. The sample size for DID and CEA is dependent on the stringency of PSM.

4.3.2. Data source

Patients' medical records

Data was extracted from the electronic medical records of all hospitalized patients admitted as inpatients to Hanbin General hospital with cerebral infarction as defined by the ICD-10 codes described in Section 4.3.2 during the study period1st June 2013 to 31st May 2017.

The list of comorbidities was adopted from Diagnosis and treatment of complications of cerebral infarction (S. zhang & wu, 2016), which outlined the common comorbidities in relation to the severity of infarction in the condition evaluation from clinical view. For instance, those patients who were sent on to a

referral hospital quickly or stayed in hospital for an unusually long time because of their particularly (generous) insurance coverage would not fit the clinical pathway

EQ-5D-3L measurement

The EQ-5D-3Lis a generic preference-based measure of HRQoL. It is a standardized, self-reported, and easy-to-use instrument which allows comparisons across health conditions and treatments. It is widely used in economic evaluation and recommended by several Health Technology Assessment (HTA) agencies around the world.

The EQ-5D-3L has been shown to be valid and responsive measure of HRQoL in stroke patients (Dorman, Waddell, Slattery, Dennis, & Sandercock, 1997; Pickard, Johnson, & Feeny, 2005). It consists of two segments, the EQ-5D descriptive system and the EQ visual analogue scale (EQ-VAS). The descriptive system consists of five single-item dimensions, each of 3 levels (Table 4-1). The EQ-VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcomes as reported by the individual respondents.

Table 4-1 EQ-5D-3L descriptive system

	No problems	**Some Problems**	**Extreme problems**
Mobility	1	2	3
Self-care	1	2	3
Usual activities	1	2	3
Pain/Discomfort	1	2	3
Anxiety/Depression	1	2	3

The EQ-5D-3L descriptive system gives a 5-digit health profile with 243 possible health states. This profile may be converted to a health state utility value using a country-specific valuation tariff. The China tariff was used to convert patient health profiles to health state utility values (Luo et al., 2017).The China valuation study was conducted in a sample of 5,939inhabitants over 15 years and older over, and the estimation relies on multi-stage, stratified, clustered random skills using the time trade-off (TTO) technique (Lang et al., 2018).

The EQ-5D-3L was administered to hospitalized patients admitted with CI from June 2013 (prior to implementation of the CP) when discharging. After implementation of the CP, the EQ-5D-3L was administered at discharge for both for CP and non-CP patients via face-to-face interviews with trained nurses.

4.3.3. Data processing

A pre-requisite for participation in the study was the implementation of an electronic prescription system within the hospital. Such a system not only facilitates the data collection for project monitoring and evaluation, but also encourages the process of physicians' behavior change.

To support efficient data linkage, all prescriptions information issued for patients participating in the CP was automatically mapped into a CP digital management module for both before and after introduction of the CP. For non-CP managed patients, all patient data could be tracked down through the routine hospital information system.

To minimize bias and ensure comparability of data across different departments of the hospital (emergency room, internal medicine department and the joint

department of Chinese & Western medicine), all data collection techniques, procedures, and data collection forms were standardized.

The most robust approach for ensuring accuracy and reliability of data collection is double data entry, where data from the entire sample is collected separately by two researchers, and compared for verification purposes before analysis. However this approach is associated with significant financial and resource costs (Büchele, Och, Bolte, & Weiland, 2005). For practical reasons, double data entry was not possible in this study. Instead, two researchers trained in the standardized extraction approach extracted data in duplicate from 5% of randomly selected records, and these data was compared to assess the overall reliability of data extraction. This process was done with the help of a junior researcher from CNHDRC.

4.4. Statistical methods

To achieve the research objectives, a mixed methods approach with three distinct analytical methods was adopted:

- Difference-in-difference analysis (DID) after propensity score matching (PSM). DID was used to calculate the change in costs and outcomes before and after intervention on groups receiving CP and standard management matched by PSM;
- Interrupted time series (ITS). ITS was used to calculate the change in costs and outcomes before and after intervention on groups receiving CP and standard management;
- Cost-effectiveness analysis (CEA) using a Markov model. Markov model was used to estimate the short and long-term cost effectiveness of the CP compared with standard management.

These methods are considered appropriate for evaluating health policy interventions with observational data (Craig et al., 2010). Taken together, these analyses will be used to assess the impact of the CP on several outcomes relevant to patients.

In order to confirm the appropriate statistical techniques, the data was first tested for normality. As the total sample size over 2,000, the Kolomogorov-Smirnov (K-S) test was used to test the normality of the continuous variables. The K-S test is an empirical distribution function in which the theoretical cumulative distribution function of the test distribution is contrasted with the empirical distribution function of the data(D, A, & E, 2006).Statistical analysis was conducted using SAS version 9.4 (SAS Institute Inc. North Carolina, USA).

4.4.1. Difference-in-difference

DID study design is commonly applied to observational data to address the absolute effect in outcomes related to the policy change (Dimick & Ryan, 2014). DID normally uses a comparison group that is experiencing the same trends but is not exposed to the policy change.

In a DID analysis, one cannot assume random assignment to avoid bias from unmeasured confounders. DID designs assume confounders that vary between groups do not vary over time and that confounders that vary over time do not vary by group. Therefore, a major assumption of DID is the parallel trends assumption, in which the trends in outcomes between the treated and comparison groups are the same prior to the intervention. See illustration of DID in Figure 4-2.

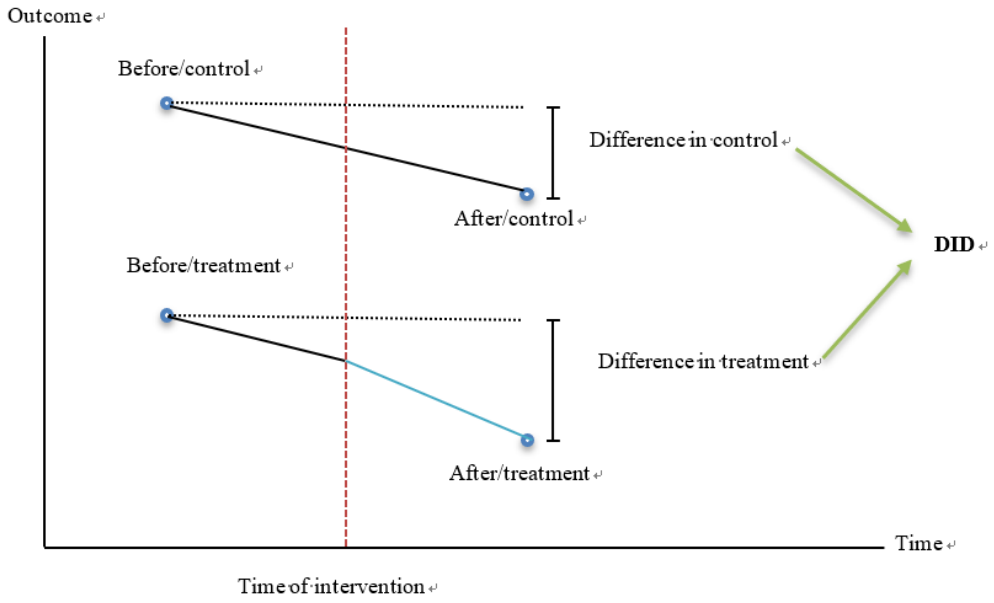

Figure 4-2 Illustration of DID

The DID analysis was carried out in support of observations of PSM-matched patients. The approach is consistent with British Medical Research Council guidelines for using natural experiments to evaluate population health interventions. The approach has been previously applied to stroke service redesign in England (Morris et al., 2014).

Total hospitalization expenses and its components (radiology expenses, laboratory testing expenses, diagnostic expenses and consultation expenses) were calculated for the four subgroups: “Before/ treatment”, “Before/ control”, “After/ treatment”; and “After/ control”. DID is employed to offset natural change before and after intervention, to allow us to state the absolute difference (the difference-in-difference) using Excel 2016 (Microsoft, Seattle USA).

Due to challenges associated with establishing causal relationships in observational research designs, a number of approaches are available to help to validate the assumptions of DID (Wing, Simon, & Bello-Gomez, 2018). In particular, this study employed PSM as described below.

4.4.2. Propensity Score Matching (PSM)

In observational studies, the assignment of treatments to intervention or control group is typically not random. When randomization is not available for treatment allocation to subjects, causal inference cannot be made as it is not possible to determine whether the differences in outcomes are attributed to the treatment itself or to unobserved differences between subjects on other characteristics (Rosenbaum & Rubin, 1983).

PSM is a statistical correction strategy for observational studies, where data bias and confounding factors potentially exist. PSM attempts to reduce, but not completely eliminate, the influence of confounding factors that could bias an estimate of the treatment effect when obtained simply by comparing outcomes among units that received the treatment versus those that did not(Austin, 2011).

PSM attempts to ensure that the treated and comparison groups have similar characteristics. The propensity score is the estimated probability for each individual in the study to be assigned to the group of interest for comparison, conditional on all observed confounders (Baek, Park, Won, Yu, & Kim, 2015). Subjects with the same or similar propensity scores can be considered to have the same or a similar distribution of all confounding variables used in constructing the propensity score.

Propensity scores are generally calculated using logistic regression, which is a model used to predict the probability that an event occurs. The propensity score is a probability, ranging in value from 0 to 1 (Rosenbaum & Rubin, 1983).

$$\ln\frac{e(x_i)}{1-e(x_i)} = \ln\frac{Pr(Z_i=1|x_i)}{1-Pr(Z_i=1|x_i)} = \alpha + \beta x_i$$

where:

$$e(x_i) = Pr(Z_i = 1|x_i)$$

and:

$$e(X_i) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \cdots + b_iX_i$$

where b_0 is the intercept; b_i are the regression coefficients; X_i are the treatment variables and covariates (random variables); x_i is the observed value of variables.

In logistic regression, the dependent variable is binary, Z_i=1 is the value for the treatment and the value for the control is Z_i=0.

Estimation of $\hat{e}(x_i)$can be expressed as:

$$\hat{e}(x_i) = \frac{1}{1 + e^{-(\widehat{b_0} + \widehat{b_1}x_1 + \widehat{b_2}x_2 + \widehat{b_3}x_3 + \cdots \widehat{b_i}x_i)}}$$

Suppose we get the value of b_i using maximum likelihood techniques, we can get a value of $\hat{e}(x_i)$ as the specific propensity score for individual subjects from either the intervention or control stream.

Once we have calculated the estimated propensity score for each subject from both CP and non-CP groups, we can match the treated subjects with subjects who have the same or most similar propensity score but did not receive treatment. (See example in Figure 4-3)

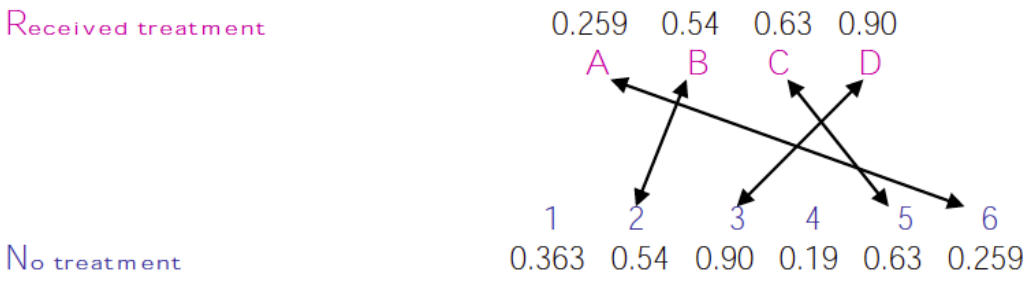

Figure 4-3 Example of PSM Nearest Neighbor Matching

This example implies the application of Nearest Neighbor Matching, where the absolute difference between the estimated propensity scores for the control and treatment groups is minimized within in certain width of caliper. Caliper means maximized value width between paired data, less width more accuracy. In this

example, the control and treatment subjects are randomly ordered. Then the first treated subject is selected along with a control subject with a propensity score closest in value to it.

$$C(P_i) = \min_j |P_i - P_j|$$

where $C(P_i)$ represents the group of control subjects j matched to treated subjectsi based on the estimated propensity score; P_i is the estimated propensity score for the treated subjects I; P_j is the estimated propensity score for the control subject j.

The PSM included patient characteristics of age, gender and severity of comorbidities. The list of comorbidities was drawn from information available in the *Diagnosis and Treatment of Complications of Cerebral Infarction*(S. zhang & wu, 2016). The matching of patients is based on the types rather than number of comorbidities.

Nearest neighbor matching without replacement, meaning that each sample being matched can only be used once, was adopted in the PSM analysis; one to one matching was selected whose caliper in our study was equal to 0.05.

Descriptive statistics summarizing the characteristics of patients included and excluded in the matching were reported for age, gender, comorbidities (diabetes, hypertension, coronary heart disease, atherosclerosis, dyslipidemia, insufficient blood supply to the brain, pulmonary infection). PSM was performed using Stata version 15.0 (Stata Corp. Texas, USA).

4.4.3. Interrupted Time Series (ITS) Analysis

ITS has been described as the "next best" approach for dealing with interventions when randomization is not possible or clinical trial data are not available" (Kontopantelis, Doran, Springate, Buchan, & Reeves, 2015). In an ITS design, data

was collected at multiple timepoints before and after an intervention is introduced to detect whether the intervention has a significant effect over and above the underlying trend.

There are several issues associated with analyzing longitudinal data (Lagarde, 2012). For example:

1) There may be a natural trend in the data that occurs independently of the event of interest or other observable events. This will result in a natural change in the outcome of interest over time.

2) Data may not meet the requirement of Ordinary Least Square (OLS) that error terms be uncorrelated. Adjacent data points in time are typically more likely to be close to each other than points that are further from each other (first-order correlation).

3) There may be regular patterns in the data due to seasonal effects. Without controlling for these changes, the real effect may be masked.

ITS allows for the statistical investigation of potential biases such as those described above in the estimate of the effect of the intervention (Ramsay et al., 2003). To detect autocorrelation, a plot of residuals against time was visually inspected. Randomly scattered residuals would suggest that there is no autocorrelation. Secondly, the Durbin–Watson statistic, was used to test for serial autocorrelation of the error terms in the regression model.

By observing a series of same outcomes at equalized-interval multiple time points before and after the introduction of an intervention, the approach aims to demonstrate the immediate and gradual effects of the intervention, given the degree to which the intervention alters the outcome of interest. The greatest benefit of this

approach is the fact that it is able to distinguish the effects attributed to intervention itself out of segmental change. It can identify whether there is an instantaneous or delayed effect; whether the impact is temporary or sustained; and whether factors other than the intervention could account for the observed interruptions.

The time period is divided into pre-intervention and post-intervention segments, and levels (intercepts) and slopes of observational outcomes are estimated in each segment, where "intercept" means the value of the observed outcomes at the beginning of a given time interval, and "slope" means the rate of change of outcomes over the time. Therefore, the "change in level" demonstrates the abrupt effect of introducing an intervention, and "change in slope" can show trend changes in the value of observed outcomes before and after the intervention. (See Figure 4-4)

The regression approach allows the statistical modeling of interrupted time series data to achieve statistical power with a relatively short time series using routinely collected observations at multiple regular time points from before and after an intervention (Lagarde, 2012). Outputs indicate the degree to which the intervention altered the outcome of interest, both immediately and over time.

The general specification of a segmented linear regression of ITS data is:

$$Y_t = \beta_0 + \beta_1 * time + \beta_2 * intervention + \beta_3 * change\ of\ slope + \varepsilon_t$$

β_0 is the intercept;β1 is the slope prior to the intervention (baseline trend), representing the change over time before the intervention was implemented;β_2 is the change in the level immediately after the intervention (level change); β_3 is the change in the slope from the pre- to post- intervention periods (trend change).The expected trend of prior to intervention, which can be seen as the comparison group in the post-intervention phase is indicated by the grey line in Figure 4-4.

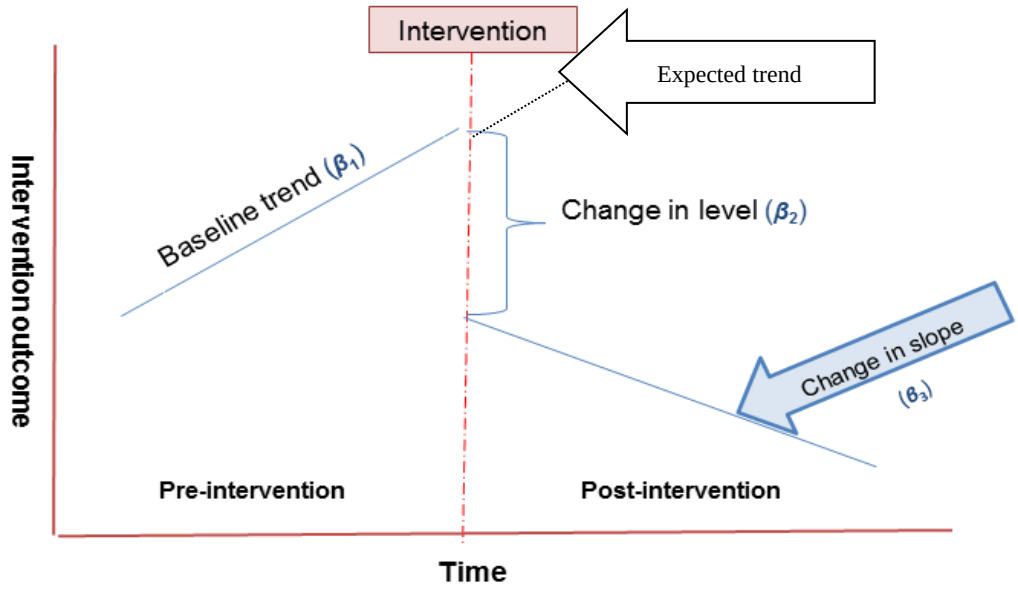

Figure 4-4 Illustration of Interrupted Time Series

There are no control counties that can be paired with the Hanbin county due to the absence of appropriate control counties unaffected by healthcare reform. Thus, the use of ITS was deemed a suitable alternative method for a situation in which randomization was not a practical option. ITS was conducted across the time periods before and after CP implementation on the monthly mean values of pre-defined outcomes (LOS, total hospitalization expenses, broken down expenses and EQ-5D-3L utility value) to describe the overall effects of the intervention.

Measurements were collected on a monthly basis over a period of four years (12 months before implementation and 36 months after implementation).

ITS was used to fit the regression models to LOS, total hospitalization expenses, and expenses related to medications, radiology, laboratory test and diagnostics, and health professional consultation time, before and after intervention.

$$Y_t = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \varepsilon_t$$

Where Y_t is the total hospitalization expenses(including medication expenses, radiology expenses, laboratory test expenses, diagnostic expenses and consultation expenses) of patients with CI in one visit; X_1 is a categorical time variable, recording the number of months between the beginning of the study and month "t" (the starting time in this study was 1st June 2013 and the ending time was 31st May 2017); X_2 is the intervention variable which is a dummy variable(X_2 =0 means before intervention, X_2 =1 means after intervention); X_3 is a categorical variable, recording the number of months of time t after intervention, X_3= 0 before intervention and X_3=X_1 after intervention. In this model, β_0 is the estimate of baseline level of outcome indicators; β_1 is the slope before intervention, that is, the estimate of monthly change of outcome indicators before intervention; β_2 is the estimate of change of level of outcome indicators after intervention compared with before intervention; β_3 is the estimate of change of slope, that is, the change of trend of outcome indicators after intervention compared with before intervention. Value of (β_1+β_3) is the slope after intervention. This model can estimate the change of intervention level and trend under the control of baseline level and trend, which is a significant advantage of piecewise regression analysis. $\mathcal{E}_t$ is the error term, which indicates that the random effects which cannot be explained by the model include the random errors of normal distribution and the error term of time (t).

Model assumptions were checked using diagnostic plots, based on the estimated residuals. An appropriate model for the data was one where residuals were independent and normally distributed having a mean of 0 and constant standard deviation. The F value and R^2 value are key indicators to check for model adequacy. In terms of the F test, by convention, a p-value smaller than 0.05, is considered acceptable. R^2 gives the percentage contribution of the independent variables to the

observed response. These tests were undertaken for each modeled outcome. Statistical analysis was performed using SAS version 9.4 and Stata version 15.0.

4.4.4. Cost-effectiveness Analysis (CEA)

CEA is employed to compare the relative costs and outcomes of an intervention to help payers and policy-makers decide whether they should implement a new technology or service (Drummond, Sculpher, Claxton, Stoddart, & Torrance, 2015). A common metric of CEA is the incremental cost-effectiveness ratio (ICER), which is calculated as the change in cost divided by the incremental effect of the new intervention compared to current standard of care.

$$ICER = \frac{Cost_{CP\ group} - Cost_{Non-CP\ group}}{Effectiveness_{\ CP\ group} - Effectiveness_{Non-CP\ group}} = \frac{\Delta Cost}{\Delta Effectiveness}$$

The ICER may be visualized on a cost-effectiveness plane as shown in Figure 4-5. Interventions falling into the bottom-right or the top-left quadrants are clearly cost-effective and cost-ineffective respectively. Interventions falling into the top-right or bottom-left quadrants may be cost effective depending on the willingness to pay (WTP) for the unit of effectiveness.

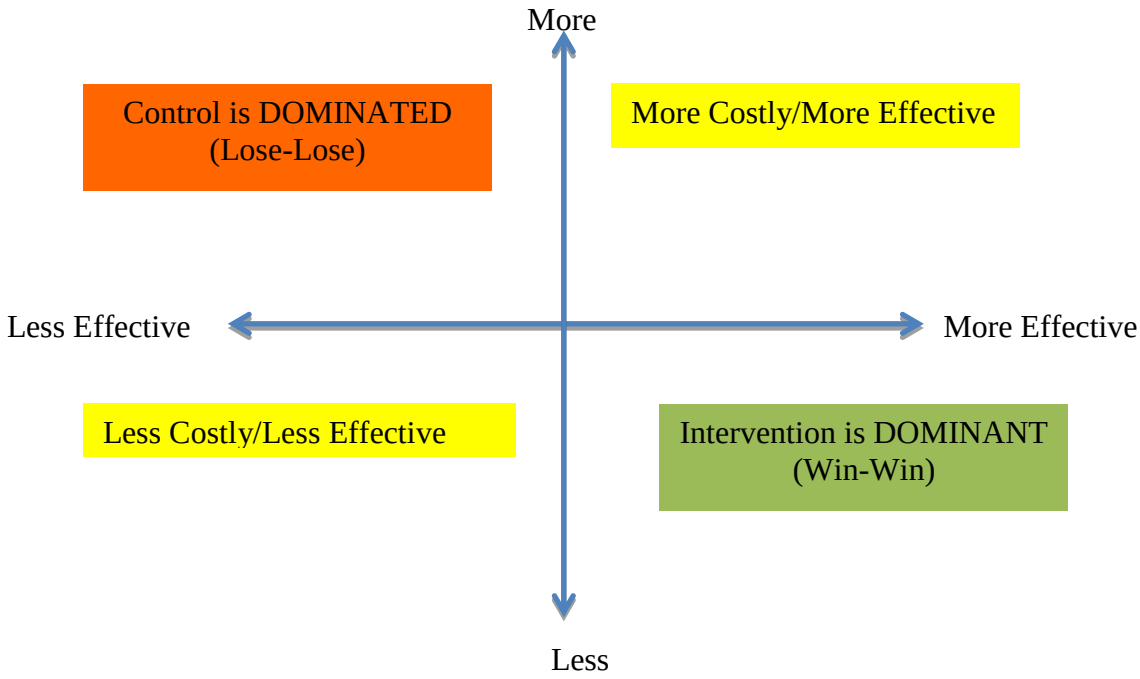

Figure 4-5 Cost-effectiveness plane

Development of model

In order to project CEA analysis and inform the decision making, steps in developing Markov model were followed as Figure 4- 6:

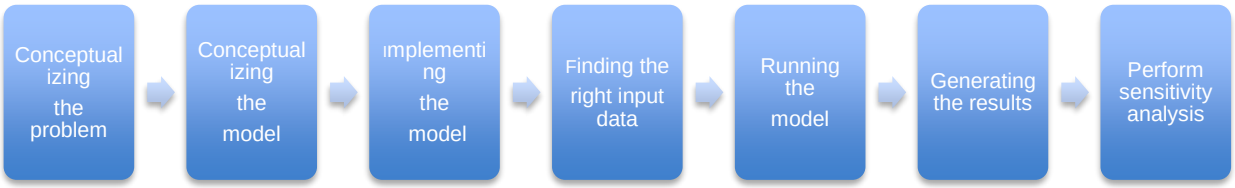

Figure 4- 6 The steps of Markov model development

In order to clarify the details of modeling, each step was processed under careful considerations and actions:

4.4.4.1. Decision problem

Target population

The analysis considered two target CI populations: “acute” inpatients and “stable” outpatients. The starting age of population is 60.

Intervention

The intervention under consideration is CP applied for CI hospitalization patients in Hanbin county.

Comparators

The comparator considered in the model is conventional treatment (non-CP management).

Outcomes

The primary outcome of interest is the ICER, as measured by incremental cost per QALY; this approach is in line with the China Pharmacoeconomics Evaluation Guideline (G. Liu, Hu, & Wu, 2011), which clarifies that a cost-utility analysis should be conducted. Additional outcomes reported include:

- Total costs
- Break-down costs
- Total QALYs

Mortality rate was excluded as outcome measure given the Chinese culture. Patients prefer to die at home rather than hospitals, which would underestimate the mortality of CI patients.

Perspective

This perspective of the analysis is that of the local Healthcare System in Hanbin County. Only direct medical costs including expenses occurred in outpatient and inpatient services of hospital and initiate project investment were considered. The analysis excludes indirect costs, the costs of lost productivity, transportation costs, etc., which occurred outside of the hospital.

Time horizon

The cost-effectiveness analysis adopts a lifetime time horizon. This approach is considered appropriate as CI can affect both mortality and morbidity, and is associated with long term sequalae. The cycle length is set to one day for inpatients in the "acute" stage, while the cycle length is one year when patients are at stable stage. The half-cycle correction had been performed.

Discounting

Costs and outcomes are discounted at 5% (G. Liu et al., 2011), which is in line with the recommendations of the China Pharmacoeconomics Evaluation Guideline.

4.4.4.2. Modelling

Model type and structure

Markov models are typically appropriate for chronic progressive conditions and have been previously applied to model stroke service redesign (Briggs, Sculpher, & Claxton, 2006; Hunter et al., 2018). The model was developed in Excel 2016 (Microsoft, Seattle USA).

As displayed in Figure 4-7 & Figure 4-8, two separate Markov simulations are used to reflect the application of CP in CI patients at acute and stable stages. This will capture the impact of CP in both short and long term. A Markov model allows patients to move between other disease management states over a fixed period of time (the Markov cycle). In line with the practice in Hanbin, patients at acute stage are included in CP based on inclusion criteria. They are discharged after the completion of CP. As the maximized LOS of hospitalized CP patients in dataset is 21 days in Hanbin, the flow between cycles in acute stage model (Figure 4-7) is determined by the probability per 1-day cycle, to transition to the next cycle (indicated by the

arrows). For patients at stable stage, the cycle length is one year (Figure 4-8).Patients in either model must be in one of three distinct and mutually exclusive disease management states: outpatient, inpatient and death.

As illustrated in Figure 4-7 & Figure 4-8, in each 1-day or 1-year cycle, the patients can either remain in the same cycle or move to the next cycle. In addition, at any cycle, patients may die and move to the death state. By definition, the model assumed that any events and transitions between disease management states occur at the end of each cycle and therefore a half cycle correction is applied. This ensured that events and movements happen, on average, in the middle of the cycle. As a result, the continuous nature of events is approximated (Sonnenberg & Beck, 1993).

The overarching result of the cost-effectiveness analysis is the combination of two Markov models, where patients at the acute stage go into hospitalization managed by CP or not. After the completion of CP, patients are discharged by the hospital and go into stable stage. This study simulates both short and long term effect of CP to estimate the overall effect of the CP management for CI patients. Disaggregated results are also illustrated to clarify results of intervention in short and long term.

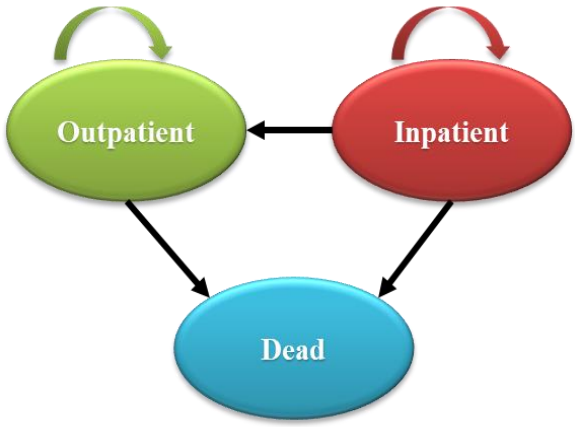

Figure 4-7 Model structure for CP application in CI patients at acute stage

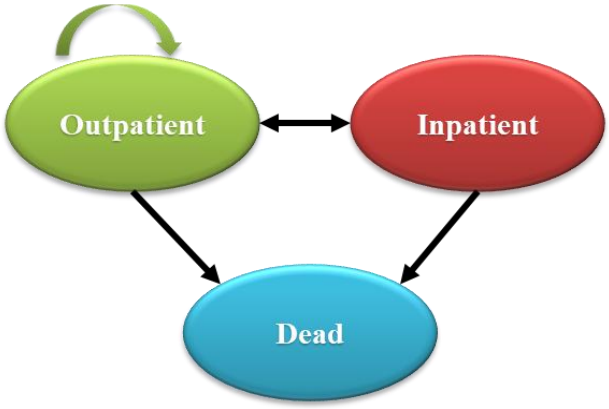

Figure 4-8 Model structure for CP application in CI patients at stable stage

Costs incurred in the outpatient state are those associated with disease treatments after discharge, which was derived from clinician consultation. These include medication expenses, radiology expenses, laboratory test expenses and consultation expenses of each visit. In the inpatient state, patients incur expenses associated with medical management, which was from PSM analysis results after intervention. These include medication expenses, radiology expenses, laboratory test expenses, consultation expenses and diagnostic expense. Death expenses are excluded based on the model's perspective.

Utilities are applied to each disease management state, which are derived from EQ-5D-3L measurement on patients in Hanbin.

4.4.4.3. Sensitivity analysis

One way sensitivity analysis

Parameter uncertainty was tested using one way sensitivity analysis. All model parameters are systematically and independently varied over a range determined by the 95% confidence interval, or +/- 20% where no estimates of precision were available. ICER was recorded at the upper and lower values to produce a tornado diagram.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was used to estimate joint parameter uncertainty. All parameters are assigned distributions and varied jointly. 1,000 Monte Carlo simulations were recorded. The distribution of parameters was known, and parameters in corresponding distribution was randomly drawn in each simulation. Results were plotted on the cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) was generated.

4.5. Discussion and potential methodological limitations

There are a number of issues and challenges that need to be considered undertaking the analysis and interpreting the findings:

- The pathways are complex interventions, which comprise not only the CP themselves, but also incentive management mechanism, training and general awareness rising on the importance of evidence-based methods. This highlights the importance of engagement with stakeholders that will help contextualize any quantitative findings and support an overall assessment of transferability.

The pathways are not completely based on clinical evidence for practical reasons – a degree of tailoring was needed to reflect local conditions and constraints. This will affect interpretation of the findings including considerations of transferability. Identifying the separate impact of the confounding factors will not be possible, although there may be some suggestive findings. This again emphasizes the importance of the qualitative analysis, given the challenges of generalizing any findings.

Chapter 5 Research findings

Summary of chapter

In this chapter, two major analytical components are introduced, which are statistical description of raw data set, and statistical analysis of selected patients. In term of statistical description, the subjects of raw data set, selection process of the appropriate patients, grouping of selected patients, and statistical test of primary outcomes are introduced sequentially. In term of statistical analysis, three major types of analysis results are reported using the approaches as descried in chapter three, which are DID after PSM, ITS, and Markov model.

5.1. Selected patient cohort

Originally, the Hanbin General hospital management extracted all the hospitalized patients' records covering the period from 1st June 2013 to 31st May 2017(12 months before and 36 months after the CP intervention time-point as 1st June 2014), whose total number of individual records is 52,328. In consideration of patient privacy, the hospital information management staff first de-identified the patient data, then processed the patient selection based on the study criteria: major diagnosis at discharge including both of infarction diagnosis description in Chinese and ICD-10 code starting with "I63", which were I63.901 (multiple cerebral infarction), I63.902 (cerebral infarction), I63.903 (lacunar infarction), and I63.301 (sequelae of cerebral infarction). The de-identified patient records were passed onto the researcher to undertake further data cleaning, in term of confirmation of diagnosis, duplication of hospitalization ID, out of date discharge data, and outlier values in specific primary outcomes.

Note that the outlier data of LOS and total hospitalization expenses, representing efficiency and expenses measurements respectively, were identified using the inter quartile range (IQR). Taking LOS as an example, the data set of LOS was sorted in increasing order and cut into 4 equal sizes as quartiles (25%, 50%, 75% and 100%), the IQR was defined as difference between highest value of Q3 and highest value of Q1 (IQR=Q3-Q1). Data falling beyond the range [lower value than Q1-1.5IQR, higher value than Q3+1.5IQR] were considered outliers and were removed from the analysis. This approach is normally applied in the statistical description of continuous variables.164 patients were removed as extreme values in term of LOS and total hospitalization expense, of which 95 patients were removed as outliers on LOS and 115 patients were removed as outliers on the total hospitalization expenses. To be noted, some outliers offended on both criteria. In terms of those patients who were removed as outliers, some of them were sufficiently severe that they were sent on to a referral hospital very quickly and recorded an extreme small number of LOS, and some of them stayed in hospital for an unusually long time because of their generous insurance coverage. Using the IQR measurement, these patients were not the target population of CP management and would have confounded evaluation of impact of the intervention. Finally, 2,533 patients were seen as the sample size for performing analysis.

The illustration of selection process of appropriate patients (also referred to as data cleaning is outlined below in Figure 5-1.

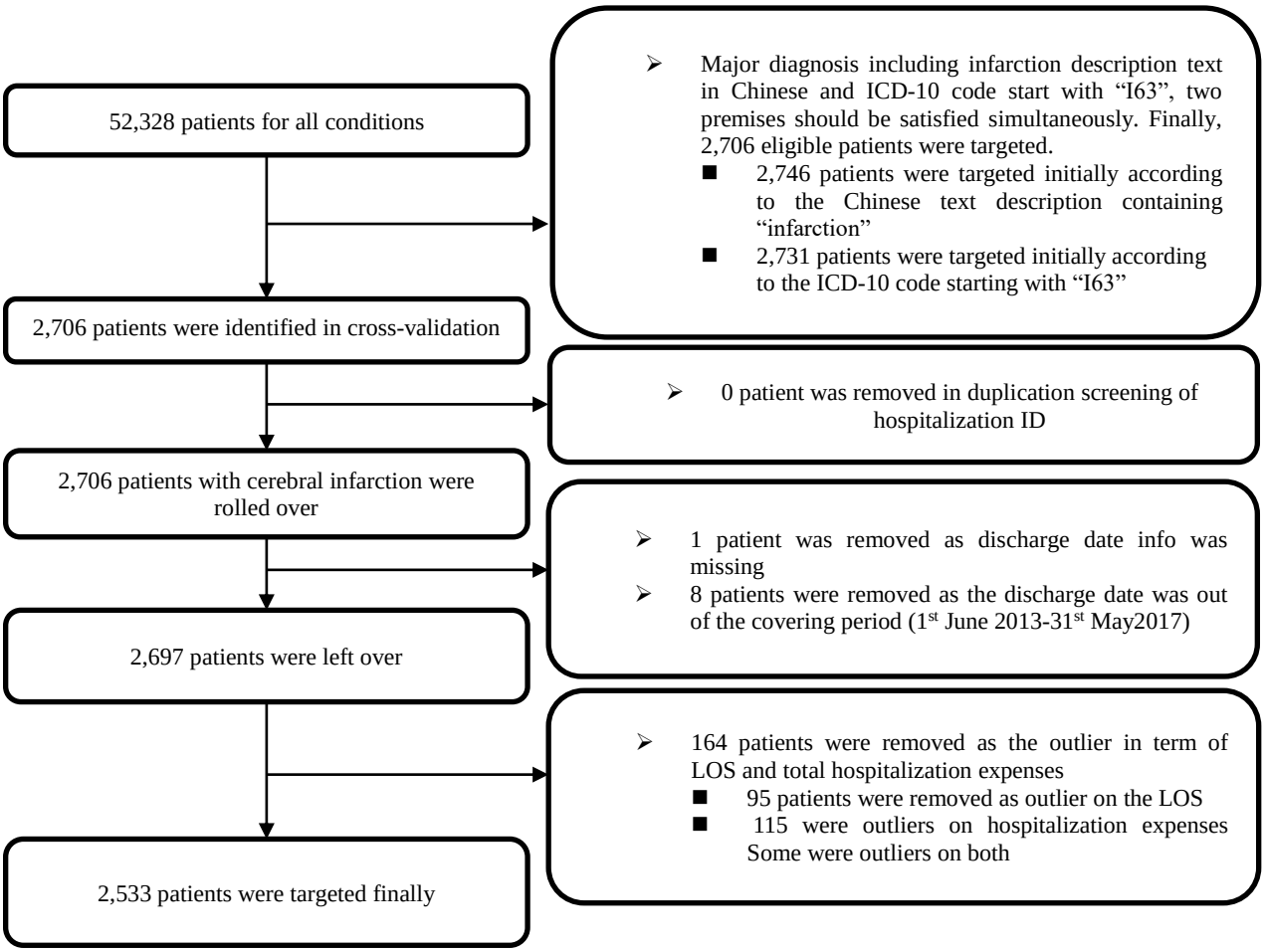

Figure 5-1 The process of data cleaning

5.1.1. Basic information about general selected patients

The descriptive summary of the selected patients can be found in Table 5-1:

Table 5-1 Descriptive summary of the selected patients

Subjects		Description	Proportion (%)
Sample size (NO. of patients)		2533	
Age (Mean ± standard deviation, Median)		66.06±9.69,66.00	
Gender	Male	1266	49.98
	Female	1267	50.02
Distribution of Department in discharge stage	Department of accident and emergency	938	37.03
	Department of Neurology	954	37.66
	Combination Department of traditional Chinese and western medicine	641	25.31
Type of health insurance	Health insurance for urban employees	107	4.22

Subjects		Description	Proportion (%)
	Health insurance for urban residence	99	3.91
	New cooperative rural insurance	2277	89.89
	Health care financial aids	14	0.55
	100% covered by employer (e.g. Public servant)	16	0.63
	100% self-payment	5	0.20
	Others	15	0.59
Comorbidities	Diabetes	196	7.74
	Hypertension	1807	71.34
	Coronary heart disease	863	34.07
	Atherosclerosis	1770	69.88
	Dyslipidemia	511	20.17
	Brain offering blood insufficiency	1344	53.06
	Pulmonary infection	125	4.93
Total hospitalization expenses (Mean ± standard deviation; Median)		4379.65±1396.15	4055.30
Medication expenses (Mean ± standard deviation; Median)		2085.70±867.15	1943.05
Radiology expenses (Mean ± standard deviation; Median)		355.76±228.07	344.39
Laboratory test expenses (Mean ± standard deviation; Median)		640.24±274.69	561.39
Consultation expenses (Mean ± standard deviation; Median)		480.39±399.52	334.68
Diagnostic expenses (Mean ± standard deviation; Median)		399.74±202.01	385.00
LOS (Mean ± standard deviation; Median)		10.88±3.70;	10
CT		1953	77.10
MRI		424	16.74
Color doppler		1670	65.93
Discharge status	Cure	61	2.41
	Improvement	2435	96.13
	Not improved	20	0.79
	Death	4	0.16
	others	13	0.51

The average age of the patient group is 66 years old, consistent with the China Stroke Prevention and Treatment Report (2015) which states that people aged over 65 has the highest risk to be admitted for infarction in China (L. Wang, Wang, & Peng, 2015). The gender distribution is balanced, although in the population at large, males

account for a larger proportion (58% vs. 42%) (L. Wang et al., 2015). In this county hospital, the CI patients were managed over three different clinical departments: the emergency department usually received acute onset patients; the Department of Neurology hosted the stable patients from outpatient or the Emergency department; and the Combination Department of traditional Chinese and western medicine provided extra rehabilitation assistance for less serious or recurrent hospitalized patients treating by Traditional Chinese Medicine (TCM). Thus, in such county hospital, the distribution of patients is diverse. In terms of the insurance type, China has not achieved universal health coverage yet, and the patient with different identity or occupation have been covered by different type of healthcare insurance. In the county areas, the NRCMS which serves rural residents dominates accounts for nearly 90% of hospitalized CI patients. In term of the expenses, the medication expenses took the largest share of total hospitalization expenses, one reason is the medication is the major approach in treatment of CI, another reason is that the clinicians have an incentive to prescribe drugs for profit-chasing. Mortality is quite low here which has two explanations, one is the patients with severe CI would be transferred upwards to an advanced level hospital, and another reason is the dying patients desired to die at home rather than in hospital, which was driven by Chinese traditional culture.

5.1.2. Grouping of selected patients

To facilitate the detection of intervention impact, the selected patients were divided into four subgroups: treatment group of patients before intervention (referred to as Before/Treatment), control group of patients before intervention (referred to as Before/Control), treatment group of patients after intervention (referred to as After/Treatment), and control group of patients after intervention (referred to as After/Control).Table 5-2 describes the number of patients in each group.

Table 5-2 Number of patients in subgroups

	Treatment	Control
Before	359	116
After	1,330	728

The number of patients in post-intervention groups is larger than pre-intervention due to different time periods of data collection (12 months before intervention and 36 months after intervention). The grouping of patients in term of before-intervention was facilitated by neurology physicians from the pilot hospital, who reviewed the patients' medical records in order to retrospectively assign patients to CP and non-CP pathways using the inclusion criteria of the CP applied in the period of after-intervention. The total sample size is 2,533 patients. The "control arm" including "before/control" and "after/control" for the purposes of this study had a total sample size is 844 patients. The "treatment arm" (patients who would have been eligible for CP management and patients who were actually managed according to the CP) had a total sample size is 1689 patients, including subgroups of "before/treatment" and "after/treatment".

5.2. Statistical description of data set

5.2.1. Normality test of selected variables

Based on the theory of cumulative distribution function, the Kolmogorov-Smirnov test (K-S test) is one of the most useful and general nonparametric tests of normality for the continuous data, which can be used to test the normality of one sample (Wikipedia, 2019c). In this study, we adopted the K-S test to verify the normality of the general sample data set of 2,533 selected patients. Accordingly, the null hypothesis H_0 of K-S test in this study is that the distribution of sample is normal. If

the p value is less than 0.05, this means the null hypothesis will be rejected and the sample data is not normally distributed. Conversely, a p value greater than 0.05 means the null hypothesis will be accepted and the sample data is normally distributed. The Shapiro-Wilk test (S-W test) is a similar nonparametric approach as K-S test to identify the normality of a sample of continuous data. The effective logic of S-W test is similar as K-S test, which provides p value. If the p value is less than 0.05, the null hypothesis of normal distribution will be rejected. Conversely, if the p value greater than 0.05, the null hypothesis will be accepted and the distribution of sample data set is normal. In statistics, the advantage of K-S test application is if the total size of sample is over 2000. If sample size less than 2000, we will perform S-W test instead.

The summaries of the normality tests were synthesized in Table 5-3.

Table 5-3 Normality test results for selected variables

Tests for Normality			**treatment arm**		**control arm**	
variable	Kolomogorov-Smirnov test		Shapiro-Wilk test		Shapiro-Wilk test	
	D	p Value	W	p Value	W	p Value
Age	0.04	<0.01	0.99	<0.0001	1.00	0.0104
length of stay	0.12	<0.01	0.94	<0.0001	0.98	<0.0001
total hospitalization expenses	0.13	<0.01	0.89	<0.0001	0.99	<0.0001
medication expenses	0.11	<0.01	0.92	<0.0001	0.98	<0.0001
Radiology expenses	0.09	<0.01	0.95	<0.0001	0.96	<0.0001
laboratory test expenses	0.12	<0.01	0.90	<0.0001	0.91	<0.0001
consultation expenses	0.14	<0.01	0.82	<0.0001	0.84	<0.0001
Diagnostic expenses	0.09	<0.01	0.95	<0.0001	0.87	<0.0001
Utility	0.15	<0.01	0.93	<0.0001	0.95	<0.0001

Clearly, the above table shows that the K-S normality tests were highly significant ($p<0.01$) for all target variables, which means the distribution of general sample is skewed. Meanwhile, a similar conclusion can be obtained for treatment arm and control arm, in which the S-W test normality tests were highly significant ($p<0.05$) for all target variables. This means the distributions of treatment arm and control arm are skewed. This is consistent with visual diagnostic of the data through histograms.

5.2.2. Significance test of selected variables for control arm and treatment arm

In here, the age, gender, type of comorbidities, consultation expenses, diagnostic expenses, laboratory test expenses, LOS, medication expenses, radiology expenses, utility values and total hospitalization expenses are all continuous data and were selected as target variables. In term of continuous variables, the Wilcoxon rank sum test should be performed to explore the significant difference between groups statistically. In term of categorical variables, the Chi square test or Fisher exact test should be performed to explore the significant difference between groups statistically. The significance difference test between control arm and treatment arm was processed and reported in Table 5-4.

Table 5-4 Significance test between control and intervention arms

		Treatment group（n=1689）		Control group(n=844)		Z/X^2 value	P Value
		N	%	N	%		
Age	mean±std,median	65.10±9.71,64.00		67.97±9.35,68.00		6.973	0.000 *
Gender						13.244	0.000 *
	Male	888	52.58%	379	44.91%		
	Female	801	47.42%	465	55.09%		
Complications							
	Diabetes	124	7.34%	72	8.53%	1.115	0.291
	Hypertension	1,241	73.48%	566	67.06%	11.323	0.001*
	Coronary heart disease	557	32.98%	306	36.26%	2.692	0.101
	Atherosclerosis	1,154	68.32%	616	72.99%	5.809	0.016 *
	Dyslipidemia	342	20.25%	169	20.02%	0.018	0.894
	Brain offering blood insufficiency	887	52.52%	457	54.15%	0.601	0.438
	Pulmonary infection	66	3.91%	59	6.99%	11.401	0.001 *
Total hospitalization expenses		4432.28±1282.95,4008.63		4274.31±1594.41,4288.09		-1.312	0.190
Medication expenses		2161.83±822.96,1943.84		1933.35±931.43,1940.10		-5.081	0.000 *
Radiology expenses		346.82±222.71,340.21		373.62±237.57,349.87		2.616	0.009 *
Laboratory test expenses		607.95±227.20,549.80		704.87±342.05,626.93		6.125	0.000*
Consultation expenses		490.72±400.44,346.00		459.73±397.11,323.95		-2.956	0.003 *
Diagnostic expenses		402.09±179.52,394.33		395.03±240.84,375.00		-2.528	0.012 *
Length of stay		11.43±3.32,11.00		9.78±4.16,10.00		-9.411	0.000 *
Utility		0.4284±0.0504,0.4356		0.2500±0.0299,0.2494		-41.081	0.000*

Note: * means the P value less than 0.05.

Based on the significance test results above, we can see that there is a statistically significant difference between treatment and control arms in terms of age, gender, hypertension, atherosclerosis, pulmonary infection (p value is less than 0.05). The control group is older, more likely to be female, and more likely to have atherosclerosis or pulmonary infection. More importantly, in term of the reporting variables, the total hospitalization expenses, and many of the components of the total, including medication expenses, radiology expenses, laboratory test expenses, consultant expenses, diagnostic expenses, LOS, utility values, are significantly different (p value is less than 0.05). Meanwhile, the mean of total hospitalization expenses in treatment arm are higher than in control arm, and LOS is longer, but the utility values of treatment arm is higher than in the control arm. To sum up, a discrepancy of baseline characteristics in two arms is observed. The corresponding distributions and description of selected variables in general cohort, control arm and treatment arm can be seen graphically in Appendix C1.

5.3. Statistical analysis of data set

Three analytical strategies were applied to estimate the impact of intervention from quantitative perspective, which are DID after PSM, ITS, and Markov model. In this part, the corresponding analytical results will be presented and described. To be emphasized, the primary outcomes in statistical analysis are: total hospitalization expenses, medication expenses, radiology expenses, laboratory test expenses, consultation expenses, diagnostic expenses, LOS and utility values. The LOS and utility values are treated as indicators of treatment quality in the analysis.

5.3.1. DID in support of PSM

5.3.1.1. Results of PSM

In order to improve the comparability of the two groups, PSM analysis was

undertaken targeting the characteristics of four grouped patients, in term of age, gender, type and number of comorbidities. The matching of patients between paired groups is in consideration of type and number of comorbidities, rather than number of comorbidities only.

Nearest neighbor matching without placement was adopted in such PSM analysis, and one to one matching was chosen whose caliper in our study equals to 0.05. The results of PSM analysis before and after can be found in the

Table 5-5 & Table 5-6.

Table 5-5 Baseline characteristics of grouped patients before intervention introduced prior to PSM

Before PSM		Treatment group（n=359）		Control group(n=116)		Z/X^2 value	P Value
		N	%	N	%		
Age	Mean ± std, median	65.57±10.08,65.00		69.70±10.74,69.50		3.521	0.000
Gender						2.994	0.084
	Male	168	46.80%	65	56.03%		
	Female	191	53.20%	51	43.97%		
Complications							
	Diabetes	31	8.64%	10	8.62%	0.000	0.996
	Hypertension	274	76.32%	75	64.66%	6.124	0.013
	Coronary heart disease	113	31.48%	35	30.17%	0.070	0.792
	Atherosclerosis	211	58.77%	66	56.90%	0.127	0.721
	Dyslipidemia	50	13.93%	19	16.38%	0.424	0.515
	Brain offering blood insufficiency	171	47.63%	55	47.41%	0.002	0.967
	Pulmonary infection	12	3.34%	11	9.48%	7.174	0.007
Total hospitalization expenses		4620.61±1296.65,4099.54		3476.98±1690.54,2901.35		-7.391	
Medication expenses		2334.87±866.78,2083.95		1611.97±977.86,1341.41		-7.388	
Radiology expenses		318.08±214.34,283.23		313.42±221.29,283.23		-0.204	
Laboratory test expenses		462.93±137.57,440.50		414.27±145.91,402.07		-3.373	
Consultation expenses		597.08±458.05,465.90		400.94±369.21,262.09		-5.175	
Diagnostic expenses		415.51±189.38,428.96		358.60±332.53,340.70		-3.625	
Length of stay		12.98±3.70,12.00		9.18±4.62,9.00		-7.764	
CT		227	63.23%	65	56.03%	1.917	
MRI		51	14.21%	15	12.93%	0.119	
Color doppler		171	47.63%	42	36.21%	4.627	

Discharge options						29.717	
	Cure	22	6.13%	3	2.59%		
	Improvement	334	93.04%	102	87.93%		
	Not improvement	1	0.28%	10	8.62%		
	Death	1	0.28%	1	0.86%		
	Others	1	0.28%	0	0.00%		
Utility		0.3492±0.0298,0.3491		0.2473±0.0295,0.2440		-16.201	

Table 5-6 Baseline characteristics of grouped patients before intervention introduced after PSM

After PSM		Treatment group（n=108）		Control group(n=108)		Z/X^2 value	P Value
		N	%	N	%		
Age	mean ± std, median	68.98±9.00,70.00		68.84±10.60,68.00		-0.109	0.913
Gender						0.297	0.586
	Male	55	50.93%	59	54.63%		
	Female	53	49.07%	49	45.37%		
Complications							
	Diabetes	11	10.19%	10	9.26%	0.053	0.818
	Hypertension	70	64.81%	71	65.74%	0.020	0.886
	Coronary heart disease	35	32.41%	35	32.41%	0.000	1.000
	Atherosclerosis	65	60.19%	64	59.26%	0.019	0.890
	Dyslipidemia	18	16.67%	17	15.74%	0.034	0.854
	Brain offering blood insufficiency	45	41.67%	49	45.37%	0.301	0.583
	Pulmonary	5	4.63%	5	4.63%	0.000	1.000

	infection						
Total hospitalization expenses		4495.66±1149.91,4081.03		3499.11±1708.93,2940.11		-5.422	
Medication expenses		2225.88±688.56,2046.77		1624.81±992.08,1341.41		-5.494	
Radiology expenses		307.40±202.22,283.23		317.84±217.44 283.23		0.229	
Laboratory test expenses		460.59±130.71,435.55		411.76±140.97,398.81		-2.932	
Consultation expenses		601.35±473.32,523.98		406.31±377.41,262.09		-3.933	
Diagnostic expenses		413.08±181.00,428.96		361.27±340.14,340.70		-2.894	
Length of stay		12.83±3.68,11.50		9.27±4.61,9.00		-5.694	
CT		74	68.52%	59	54.63%	4.403	
MRI		11	10.19%	15	13.89%	0.700	
Color doppler		51	47.22%	39	36.11%	2.743	
Discharge options						9.798	
	Cure	7	6.48%	2	1.85%		
	Improvement	100	92.59%	98	90.74%		
	Not improvement	0	0.00%	7	6.48%		
	Death	1	0.93%	1	0.93%		
	Others	0	0.00%	0	0.00%		
Utility		0.3490±0.0283,0.3511		0.2475±0.0292,0.2440		-12.699	

Table 5-5 & Table 5-6 showed the baseline characteristics of grouped patients ("Before/treatment" subgroup and "Before/control" subgroup) before and after the applying of PSM approach. Following application of PSM (Table 5-6), there were no statistically significant differences between the matched pairs of patients in the "Before/treatment" subgroup and the "Before/control" subgroup by age, gender and type and number of comorbidities. The application of PSM has allowed for potential confounding caused by observable characteristics to be eliminated.

The illustration of the matching patients before intervention introduced can be seen in Figure 5-2.

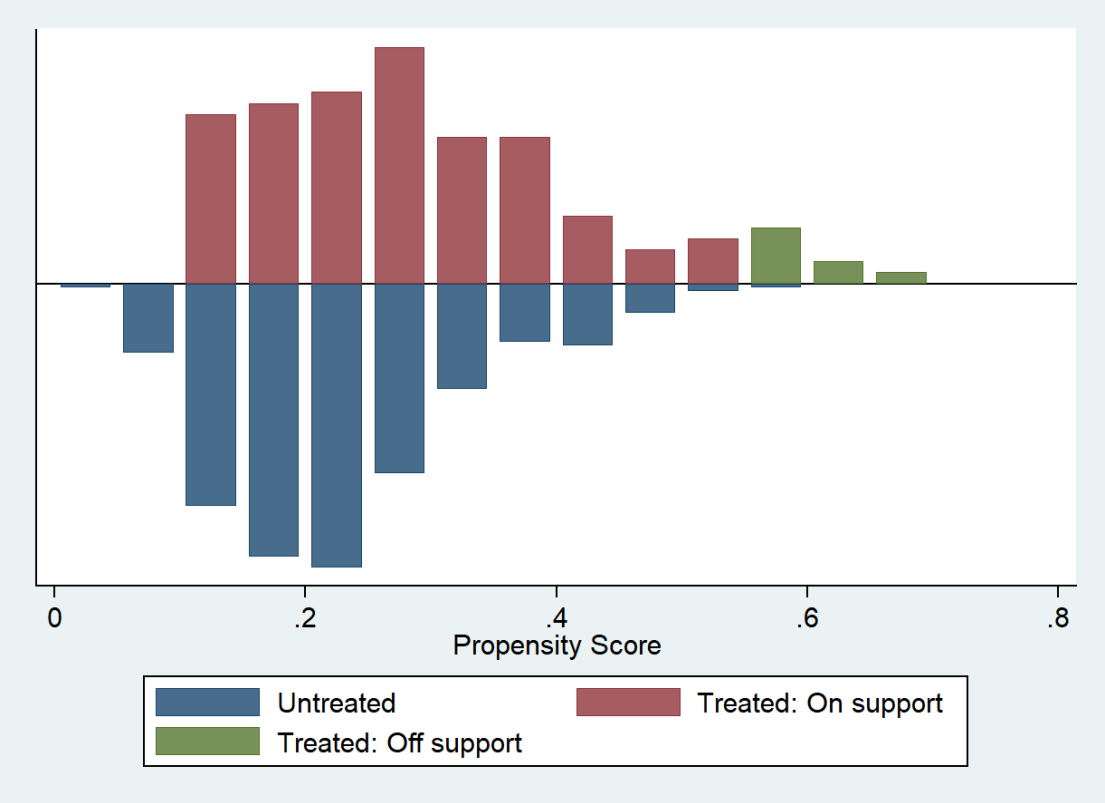

Figure 5-2 The result of PSM for stage of before intervention

In the above figure, the blue areas ("Untreated" defined by statistics software automatically) indicate the 108 paired patients used for matching out of 359 CI patients in group of "Before/Treatment", who would have been eligible for the CP.

The red areas (“Treated: on support” defined by statistics software automatically) indicate the 108 paired patients out of 116 infarction patients who were not eligible for CP. The green area (“Treated: off support” defined by statistics software automatically) means the unpaired patients in the group of “Before/Control”. In general, we can see symmetry between the blue and red areas, which indicates the effectiveness of matching.

Table 5-7 Baseline characteristics of grouped patients after intervention introduced prior to PSM

Before PSM		Treatment group（n=1330）		Control group(n=728)		Z/X^2 value	P Value
		N	%	N	%		
Age	Mean ± std, median	64.97±9.60,64.00		67.69±9.08,67.00		6.285	0.000
Gender							
	Male	633	47.59%	400	54.95%	10.170	0.001
	Female	697	52.41%	328	45.05%		
Complications							
	Diabetes	93	6.99%	62	8.52%	1.569	0.210
	Hypertension	967	72.71%	491	67.45%	6.306	0.012
	Coronary heart disease	444	33.38%	271	37.23%	3.063	0.080
	Atherosclerosis	943	70.90%	550	75.55%	5.102	0.024
	Dyslipidemia	292	21.95%	150	20.60%	0.509	0.476
	Brain offering blood insufficiency	716	53.83%	402	55.22%	0.364	0.546
	Pulmonary infection	54	4.06%	48	6.59%	6.409	0.011
Total hospitalization expenses		4381.45±1274.95,3951.39		4401.35±1542.10 ,4379.48		1.792	
Medication expenses		2115.12±804.71,1907.76		1984.56±914.12,1996.05		-1.990	
Radiology expenses		354.59±224.36,344.39		383.22±238.81,349.87		2.669	
Laboratory test expenses		647.09±230.76,585.56		751.18±341.58, 678.13		6.251	
Consultation expenses		462.01±378.51,322.41		469.10±400.81,333.09		-0.599	
Diagnostic expenses		398.47±176.67,387.57		400.83±222.53,375.00		-0.837	
Length of stay		11.02±3.08,10.00		9.87±4.07,10.00		-6.092	
CT		1,053	79.17%	608	83.52%	5.701	
MRI		252	18.95%	106	14.56%	6.301	
Color doppler		933	70.15%	524	71.98%	0.760	

Discharge options						44.968	
	Cure	28	2.11%	8	1.10%		
	Improvement	1,302	97.89%	697	95.74%		
	Not improvement	0	0.00%	9	1.24%		
	Death	0	0.00%	2	0.27%		
	Others	0	0.00%	12	1.65%		
Utility		0.4497±0.0290,0.4491		0.2504±0.0300,0.2496		-37.560	

Table 5-8 Baseline characteristics of grouped patients after intervention introduced after PSM

After PSM		Treatment group（n=724）		Control group(n=724)		Z/X^2 value	P Value
		N	%	N	%		
Age	Mean ± std, median	68.17±8.83,67.00		67.62±9.05,67.00		-1.056	0.291
Gender						0.400	0.527
	Male	384	53.04%	396	54.70%		
	Female	340	46.96%	328	45.30%		
Complications							
	Diabetes	51	7.04%	62	8.56%	1.161	0.281
	Hypertension	487	67.27%	490	67.68%	0.028	0.866
	Coronary heart disease	274	37.85%	268	37.02%	0.106	0.745
	Atherosclerosis	550	75.97%	546	75.41%	0.060	0.806
	Dyslipidemia	133	18.37%	150	20.72%	1.269	0.260
	Brain offering blood insufficiency	419	57.87%	399	55.11%	1.124	0.289
	Pulmonary infection	45	6.22%	44	6.08%	0.012	0.913
Total hospitalization		4447.79±1287.62,4005.99		4400.85±1545.32,4376.51		0.612	radiolog

expenses							y
Medication expenses		2136.68±806.95,1936.80		1983.96±916.19,1996.05		-2.426	
Radiology expenses		354.85±218.96,344.39		383.73±238.59,349.87		2.190	
Laboratory test expenses		666.32±245.28,612.53		750.12±341.57,677.33		4.212	
Consultation expenses		483.50±395.01,337.16		469.92±401.70,333.95		-1.460	
Diagnostic expenses		392.70±172.54,386.21		400.96±222.36,375.00		-0.284	
Length of stay		11.18±3.14,10.00		9.89±4.07,10.00		-6.009	
CT		563	77.76%	604	83.43%	7.423	
MRI		133	18.37%	106	14.64%	3.653	
Color doppler		497	68.65%	521	71.96%	1.905	
Discharge options						25.949	
	Cure	18	2.49%	8	1.10%		
	Improvement	706	97.51%	694	95.86%		
	Not improvement	0	0.00%	9	1.24%		
	Death	0	0.00%	2	0.28%		
	Others	0	0.00%	11	1.52%		
Utility		0.4500±0.0296,0.4496		0.2503±0.0300,0.2494		-32.943	

Comparing before and after PSM, we can see that the samples are more balanced after PSM. Prior to PSM, age, gender, hypertension, atherosclerosis and pulmonary infection are significantly different (p value less than 0.05) in the two groups (see

Table 5-7). After adjusting with PSM, these differences are no longer significant (see Table 5-8).Then we are confident to say that the patients in two subgroups are comparable, and observable confounding factors between the two groups were eliminated.

The illustration of the matching patients after intervention introduced can be seen in Figure 5-3.

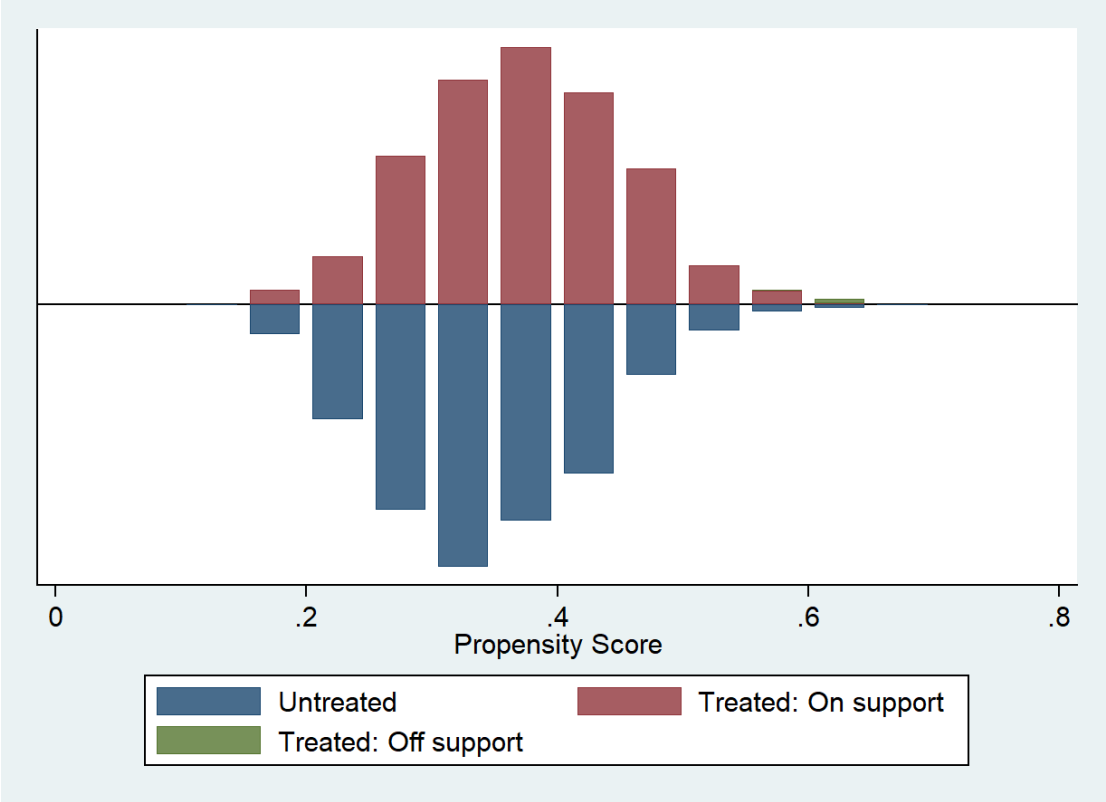

Figure 5-3 The result of PSM for stage of after intervention

In the above figure, the blue areas ("Untreated" defined by statistics software automatically) indicate the 724 paired patients out of 1,330 CI patients ingroup of "After/Treatment", who are managed by CP approach after the intervention was introduced. The red areas ("Treated: on support" defined by statistics software automatically) indicate the 724 paired patients out of 728 CI patients in group of "After/Control", which means the intended patients were not eligible to be managed by CP approach after intervention introduced. The green area ("Treated: off support"

defined by statistics software automatically) means the unpaired patients in the group of “After/Control”. In general, we can see symmetry between the blue and red areas, which indicates the effectiveness of matching.

5.3.1.2. Results of DID analysis

Using the PSM samples, DID analysis was undertaken on the outcome variables listed in section 2.3.2 . The summary of DID results are shown in Table 5-9 to Table 5-16.

Table 5-9 DID result of mean total hospitalization expenses (YUAN)

Total hospitalization expenses	Treatment group	Control group	difference
Before	4495.66	3499.11	996.55
After	4447.79	4400.85	46.94
difference	47.87	-901.74	949.61

As shown in the above table, for the control group, hospitalization expenses increased by 901.74 YUAN. In contrast, for the CP managed patients, hospitalization expenses decreased by 47.87 YUAN after the intervention was introduced. We cannot say that all the differences may be attributed to the intervention. Employing DID to offset the natural trend in the control group before and after intervention, we can state that the absolute difference attributed to CP intervention is estimated at 949.61 YUAN, which means the patients managed by CP approach will save 949.61 YUAN per patient on average, compared to non-CP managed patients. The next investigation is how the difference in total expenses breaks down among the five expenditure components of total hospitalization expenses.

Table 5-10 DID result of medication expenses (YUAN)

Medication expenses	Treatment group	Control group	difference
Before	2225.88	1624.81	601.07
After	2136.68	1983.96	152.72

difference	89.20	-359.15	448.35

As shown in the above table, for the control group, medication expenses would increase by 359.15 comparing the period before and after the intervention. In comparison, for the treatment group medication expenses would decrease by 89.20 YUAN comparing the period before and after the intervention. We cannot say that all the differences may be attributed to the intervention. Employing DID to offset the natural trend in the control group before and after intervention, we can state that the absolute difference attributed to CP intervention is estimated at 448.35 YUAN, which means the patients managed by CP approach will save 448.35 YUAN per patient on average, compared to non-CP managed patients.

Table 5-11 DID result of Radiology expenses (YUAN)

Radiology expenses	**Treatment group**	**Control group**	**difference**
Before	307.4	317.84	-10.44
After	354.85	383.73	-28.88
difference	-47.45	-65.89	18.44

As shown in the above table, for the control group, radiology expenses would increase by 65.89 comparing the period before and after the intervention. In comparison, for the treatment group radiology expenses would increase by 47.45 YUAN comparing the period before and after the intervention. We cannot say that all the differences may be attributed to the intervention. Employing DID to offset the natural trend in the control group before and after intervention, we can state that the absolute difference attributed to CP intervention is estimated as 18.44YUAN, which means the patients managed by CP approach will save 18.44YUAN per patient on average, compared to non-CP managed patients.

Table 5-12 DID result of laboratory test expenses (YUAN)

Laboratory test expenses	**Treatment group**	**Control group**	**difference**
Before	460.59	411.76	48.83

After	666.32	750.12	-83.8
difference	-205.73	-338.36	132.63

As shown in the above table, for the control group, laboratory test expenses would increase by 338.36 comparing the period before and after the intervention. In comparison, for the treatment group laboratory test expenses would increase by 205.73YUAN comparing the period before and after the intervention. We can state that the absolute difference attributed to CP intervention is estimated as 132.63 YUAN, which means the patients managed by CP approach will save 132.63 YUAN per patient on average, compared to non-CP managed patients.

Table 5-13 DID result of consultation expenses (YUAN)

Consultation expenses	**Treatment group**	**Control group**	**difference**
Before	601.35	406.31	195.04
After	483.5	469.92	13.58
difference	117.85	-63.61	181.46

As shown in the above table, for the control group, consultation expenses would increase by 63.61 comparing the period before and after the intervention. In comparison, for the treatment group consultation expenses would decrease by 117.85 YUAN comparing the period before and after the intervention. We can state that the absolute difference attributed to CP intervention is estimated at 181.46 YUAN, which means the patients managed by CP approach will save 181.46 YUAN per patient on average, compared to non-CP managed patients.

Table 5-14 DID result of diagnosis expenses (YUAN)

Diagnostic expenses	**Treatment group**	**Control group**	**difference**
Before	413.08	361.27	51.81
After	392.7	400.96	-8.26
difference	20.38	-39.69	60.07

As shown in the above table, for the control group, diagnostic expenses would increase by 39.69 comparing the period before and after the intervention. In comparison, for the treatment group diagnostic expenses would decrease by 20.38

YUAN comparing the period before and after the intervention. We can state that the absolute difference attributed to CP intervention is estimated at 60.07 YUAN, which means the patients managed by CP approach will save 60.07 YUAN per patient on average, compared to non-CP managed patients.

In term of expenses, the saving of total hospitalization expenses for the intervention group can be broken down into following subjects, visually in a pie chart as:

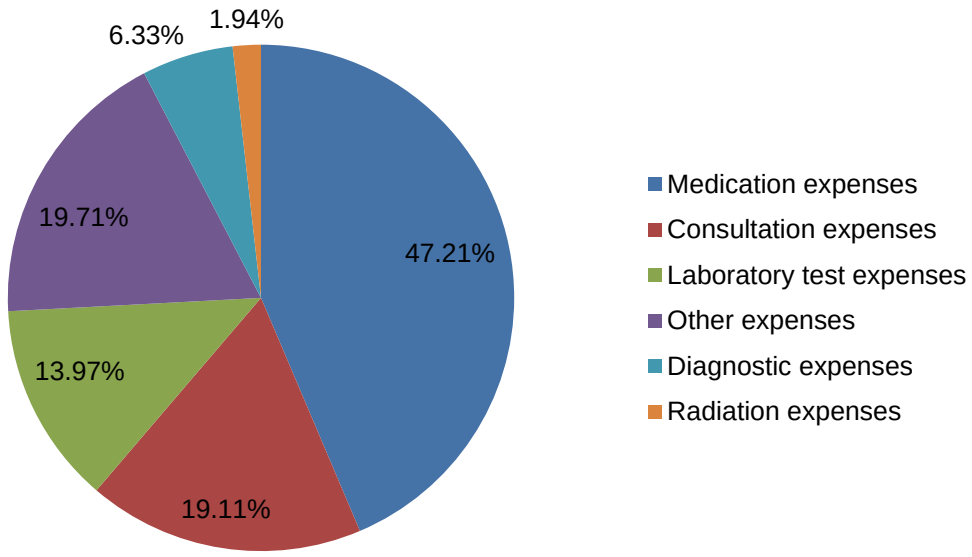

Figure 5-4 Proportion of total hospitalization expenses savings

The most saving of hospitalization are due to saving of medication expenses, accounting for 47.21%. The consultation expenses, laboratory test expenses were also reduced significantly. In contrast, the diagnostic expenses and radiology expenses did not change noticeably, accounting for 6.33% and 1.94% respectively. See Figure 5-4.

Table 5-15 DID result of LOS (days)

Length of stay	**Treatment group**	**Control group**	**difference**
Before	12.83	9.27	3.56
After	11.18	9.89	1.29
difference	1.65	-0.62	2.27

As shown in the above table, for the control group, LOS would increase by 0.62 day comparing the period before and after the intervention. In comparison, for the treatment group medication expenses would decrease by 1.65 days comparing the period before and after the intervention. We can state that the absolute difference attributed to CP intervention is estimated as 2.27 days, which means the patients managed by CP approach will save 2.27 days per patient on average, compared to non-CP managed patients.

Table 5-16 DID result of EQ-5D-3L (utility value)

Utility	Treatment group	Control group	Difference
Before	0.3490	0.2475	0.1015
After	0.4500	0.2503	0.1997
difference	-0.1010	-0.0028	-0.0982

As shown in the above table, for the control group, average utility score would increase by 0.0028 comparing the period before and after the intervention. In comparison, for the treatment group utility score would increase by 0.1010 comparing the period before and after the intervention. We can state that the absolute difference attributed to CP intervention is estimated as 0.0982, which means the patients managed by CP approach will obtain more utility score of 0.0982 on average, compared to non-CP managed patients.

5.3.2. Results of ITS

As described in chapter3, ITS was used to explore the intervention impact using monthly equal-interval data. According to the grouping of patients in Table 5-2, all patients before and after the intervention (including those not managed by the CP) were analyzed so that the sample size of the “Before” group is 475 (12 months data), and the sample size of the “After” group is 2,058 (36 months of data). Patient data before intervention were grouped into 12 monthly interval subgroups based on

patients' discharge date, and 36 monthly interval subgroups after intervention, which is from 1st June 2014 to 31st May 2017.To investigate the relatively short impact of CP, the comparison between 12 months before and after was conducted as well, results can be provided upon request. In addition, patients in "Before/Treatment" was informed by clinical guideline, which is considered a confounding factor of CP. Therefore, the group of patients refer to "Before/Control" and "After/Treatment" were compared, and results are positive which implies that CP treatment save money and improves quality of care. Such results can be provided upon request. This chapter will only discuss about results of ITS for all patients before and after CP intervention, to investigate the overarching impact of CP.

Un-matched patient level data was used in ITS as PSM cannot be applied to monthly patient-level subgroup data. In addition, the ITS is workable on continuous variables, thus the outcome measures which are continuous variables are included in the following analysis: LOS, total hospitalization expenses, medication expenses, radiology expenses, laboratory test expenses, consultation expenses, diagnostic expenses and EQ-5D-3L based utility values. In each monthly timepoint, mean value of each outcome measure is calculated to process the ITS analysis.

Before developing the multiple linear regression model described in section 4.4.3, model assumptions should be examined This was done using diagnostic plots, which are based on the estimated residuals.

Length of Stay

In general, the CP intervention had a positive impact on LOS by reducing average LOS and variations. This is consistent with aforementioned DID result. As indicated in Figure 5-5, there is increasing trend of LOS before CP intervention and

decreasing trend after CP intervention. Meanwhile, the variability of the plots shown in Figure 5-5 was reduced after intervention. According to

Table 5-17, we can see the p value is <.0001, which is statistically significant using 0.05 as standard. However, none of the parameters are statistically significant. Statistical results show limited effect of CP.

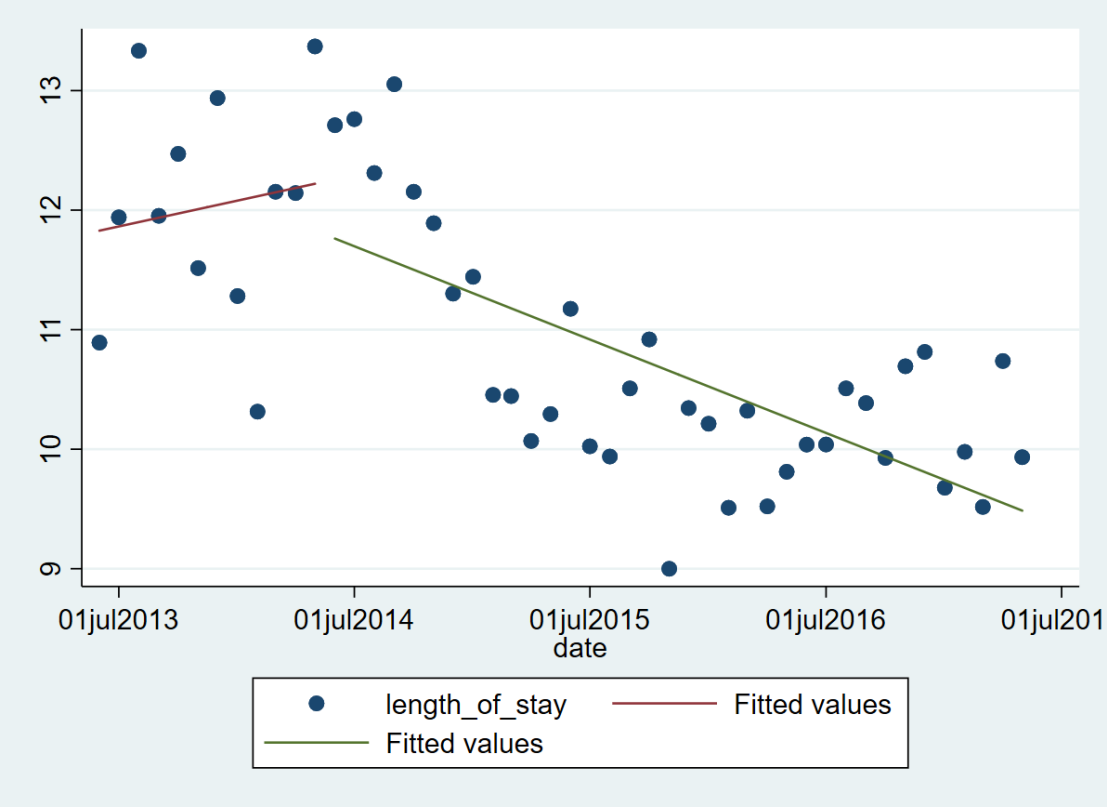

Figure 5-5 Linear regression graph of LOS

Table 5-17 Linear regression simulation test result of LOS

Variables	Estimated Parameter	Standard Deviation	P value
Intercept	11.79	0.49	<.0001
X1	0.04	0.07	0.584
X2	0.82	0.64	0.2051
X3	-0.10	0.07	0.1398
R^2	0.5527		<.0001

X^1: slope prior to the intervention (Baseline trend)
X^2: change in the level immediately after the intervention (level change)
X^3: change in the slope from the pre-to-post intervention periods (trend change)

EQ-5D-3L based utility value

In general, the index utility value after CP intervention is higher than before, which is in line with the DID result. However, index scores appear to decline over time to levels prior to the introduction of the CP (see Figure 5-6). The increase in index value on introduction of the CP was 0.1366 (p<.0001) compared with before. The decreasing trend is statistically significant (see Table 5-18). Patients were getting a lot of attention early on because of the introduction of the CP (the physicians and hospitals wanted to make it a success – maybe there were also getting more standardized treatment, medicines, necessary laboratory test etc.) This relative attention to patient needs may have declined over time as the CP became more routine.

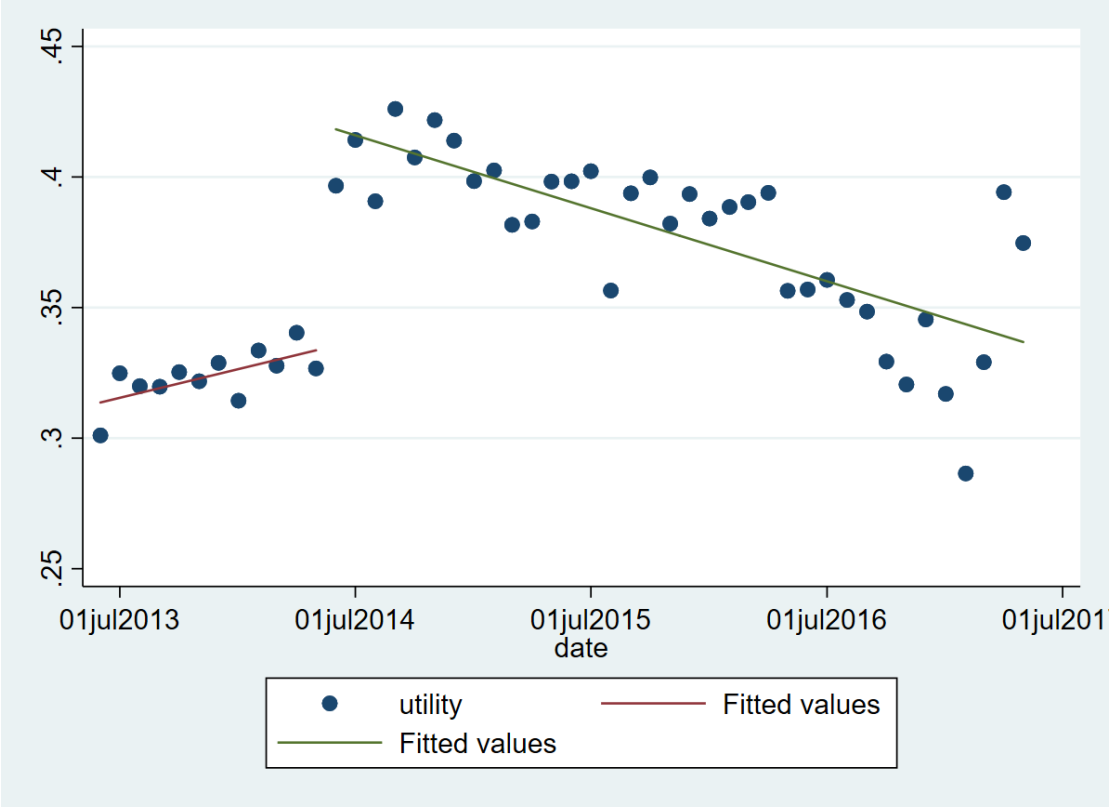

Figure 5-6 Linear regression graph of EQ-5D-3L based utility value

Table 5-18 Linear regression simulation test result of EQ-5D-3L based utility value

Variables	Estimated Parameter	Standard Deviation	P value

Intercept	0.3119	0.0119	<.0001
X^1	0.0018	0.0016	0.2665
X^2	0.1366	0.0155	<.0001
X^3	-0.0042	0.0016	0.0154
R^2	0.7435		<.0001

X^1: slope prior to the intervention (Baseline trend)
X^2: change in the level immediately after the intervention (level change)
X^3: change in the slope from the pre-to-post intervention periods (trend change)

Total hospitalization expenses

CP impact on the total hospitalization expenses is not clear based on the results. As indicated in Figure 5-7, there is an abrupt increase after CP intervention. The total hospitalization expenses decreased in 2015, and increased again in 2016. However, the trend is decreasing in general. All parameters are not significant according to Table 5-19. Statistical results show limited effect of CP.

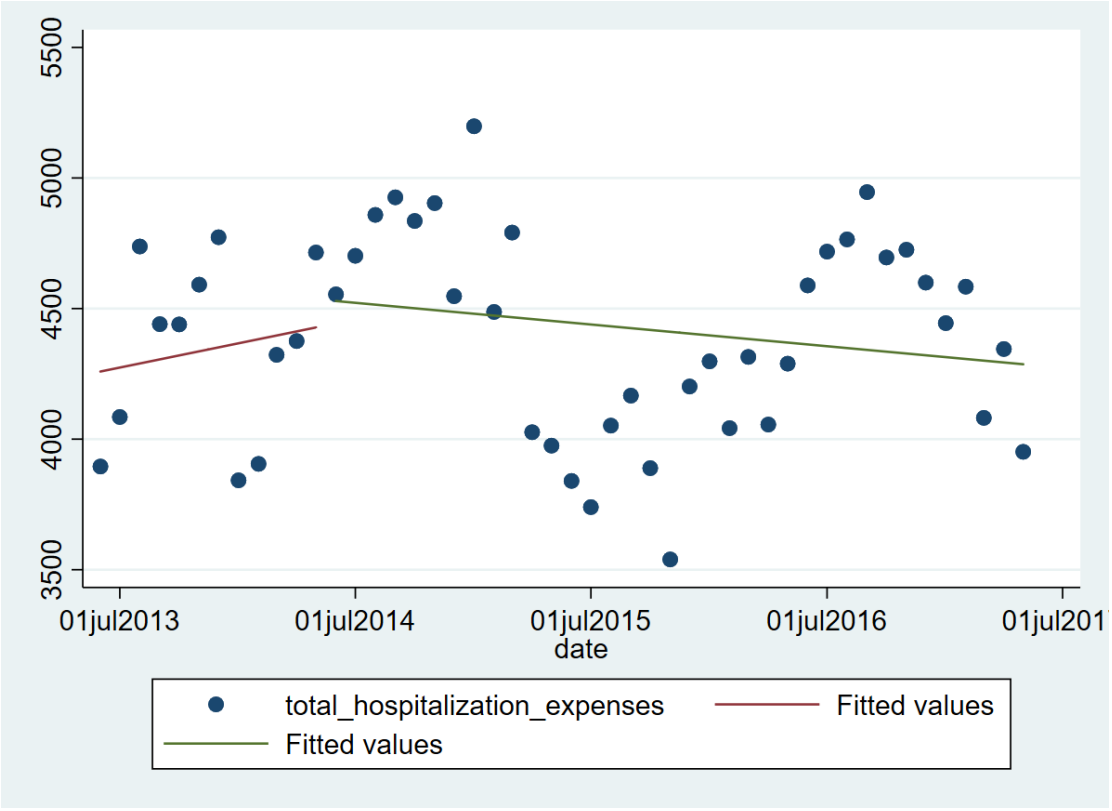

Figure 5-7 Linear regression graph of total hospitalization expenses

Table 5-19 Linear regression simulation test result of total hospitalization

expenses			
Variables	**Estimated Parameter**	**Standard Deviation**	**P value**
Intercept	4242.68	238.65	<.0001
X^1	15.53	32.43	0.6344
X^2	377.17	311.66	0.2327
X^3	-22.48	33.02	0.4995
R^2	0.0377		0.6345

X^1: slope prior to the intervention (Baseline trend)
X^2: change in the level immediately after the intervention (level change)
X^3: change in the slope from the pre-to-post intervention periods (trend change)

Medication expenses

As shown in Figure 5-8, findings are similar to the analysis undertaken on hospitalization expenses, there is an abrupt increase after CP intervention, and decrease in 2015, it goes up again in 2016. However, the trend is decreasing in general. Table 5-20 shows that the p value of regression is 0.3251, which is considered to be not significant under the standard of 0.05. It indicates limited explanatory power of results reflected by the graph.

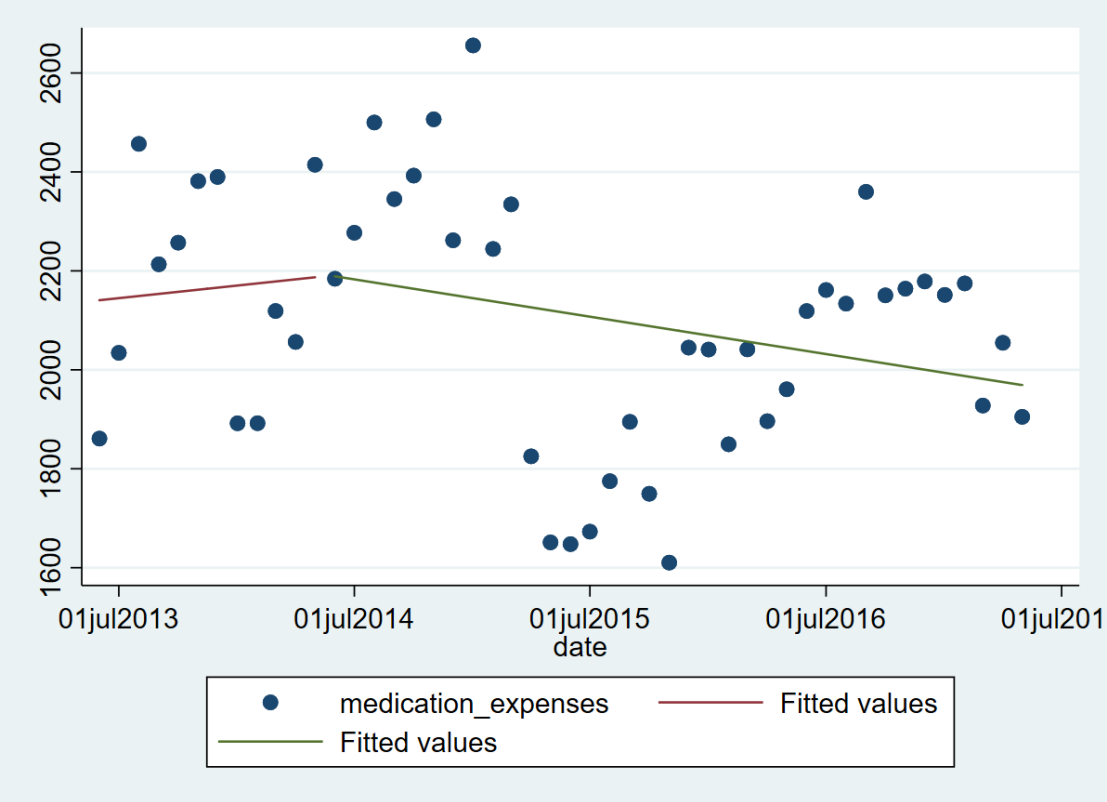

Figure 5-8 Linear regression graph of medication expenses

Table 5-20 Linear regression simulation test result of medication expenses

Variables	Estimated Parameter	Standard Deviation	P value
Intercept	2136.08	153.75	<.0001
X^1	4.30	20.89	0.838
X^2	135.45	200.79	0.5035
X^3	-10.61	21.27	0.6205
R^2	0.075		0.3251

X^1: slope prior to the intervention (Baseline trend)
X^2: change in the level immediately after the intervention (level change)
X^3: change in the slope from the pre-to-post intervention periods (trend change)

Radiology expenses

Radiology expenses are higher than that before the CP intervention, but the trend is decreasing after the CP intervention (Figure 5-9). Table 5-21 shows that the p value of regression is 0.0356, which is considered to be significant under the standard of 0.05. Changes in level and slope, were however not statistically significant. It indicates limited explanatory power of results reflected by the graph.

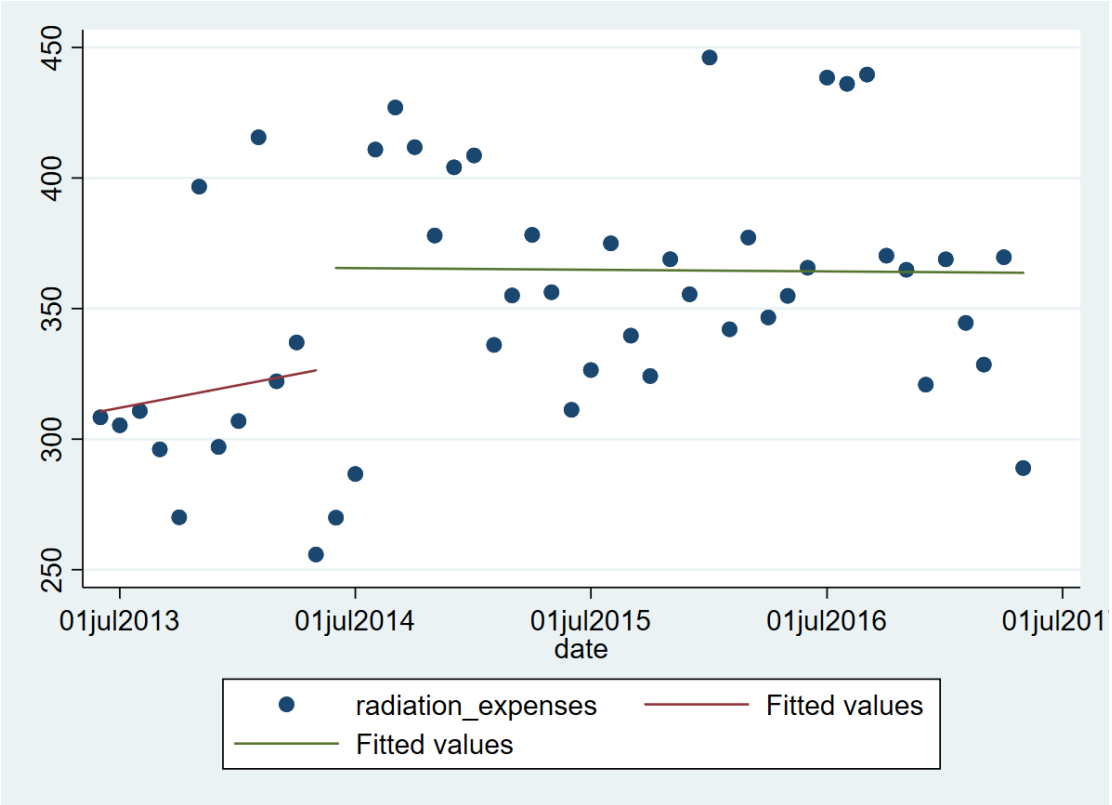

Figure 5-9 Linear regression graph of radiology expenses

Table 5-21 Linear regression simulation test result of radiology expenses

Variables	Estimated Parameter	Standard Deviation	P value
Intercept	309.50	28.08	<.0001
X1	1.38	3.81	0.7187
X2	56.80	36.66	0.1285
X3	-1.44	3.88	0.7131
R^2	0.1752		0.0356

X^1: slope prior to the intervention (Baseline trend)
X^2: change in the level immediately after the intervention (level change)
X^3: change in the slope from the pre-to-post intervention periods (trend change)

Laboratory test expenses

The results show that laboratory test expenses continue to increase after CP introduction; the post intervention slope suggests that it is at a slower rate rather than before the CP, but this is not statistically significant (see Figure 5-10 and Table 5-22). Table 5-22 shows R^2 to be 0.83 (p<.0001). Laboratory test expenses increased 118.58 YUAN after CP intervention (p=0.0147).

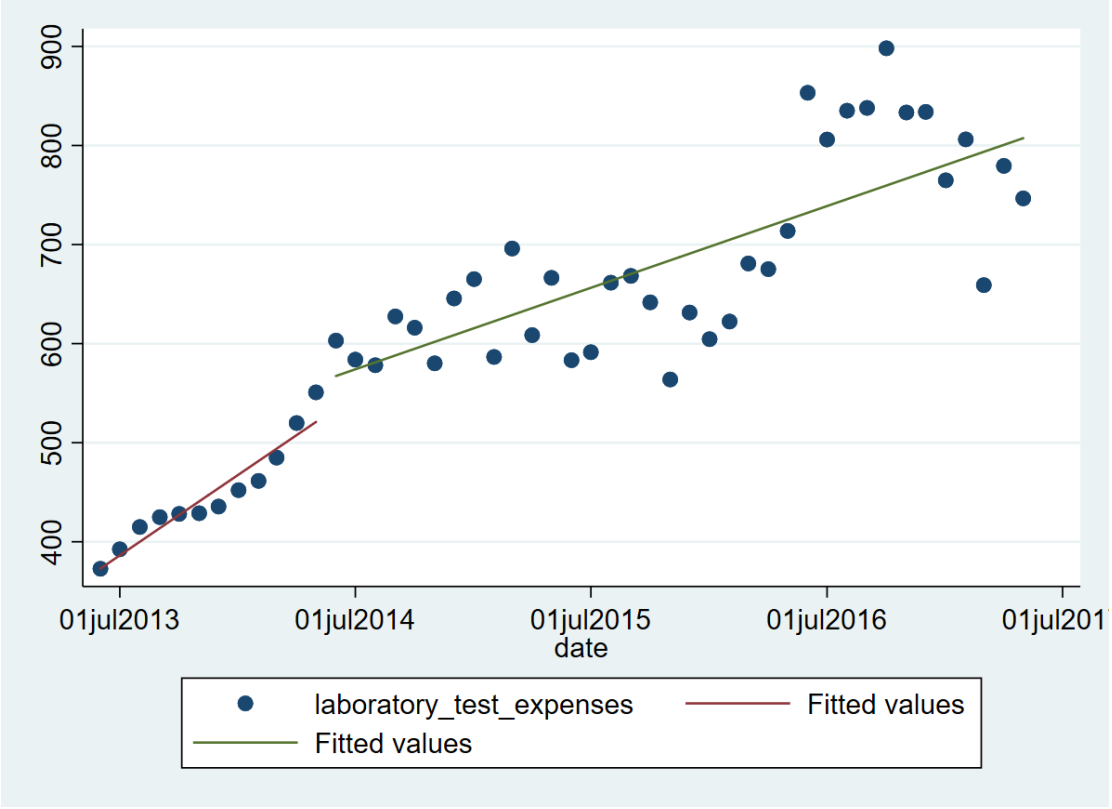

Figure 5-10 Linear regression graph of laboratory test expenses

Table 5-22 Linear regression simulation test result of laboratory test expenses

Variables	Estimated Parameter	Standard Deviation	P value
Intercept	359.59	35.74	<.0001
X^1	13.48	4.86	0.008
X^2	118.58	46.67	0.0147
X^3	-6.62	4.94	0.1874
R^2	0.8308		<.0001

X^1: slope prior to the intervention (Baseline trend)
X^2: change in the level immediately after the intervention (level change)
X^3: change in the slope from the pre-to-post intervention periods (trend change)

Consultation expenses

As shown in Figure 5-11, fitted trend line appears to show a change in slope post the introduction of CP, the variation of scatters are less after the CP intervention. In general, it shows CP intervention generally decreases consultation expenses. Table 5-23 shows that the p value of regression is 0.0007, which is considered to be statistically significant under the standard of 0.05. However, other parameters in the

regression are not statistically significant. Statistical results show limited effect of CP.

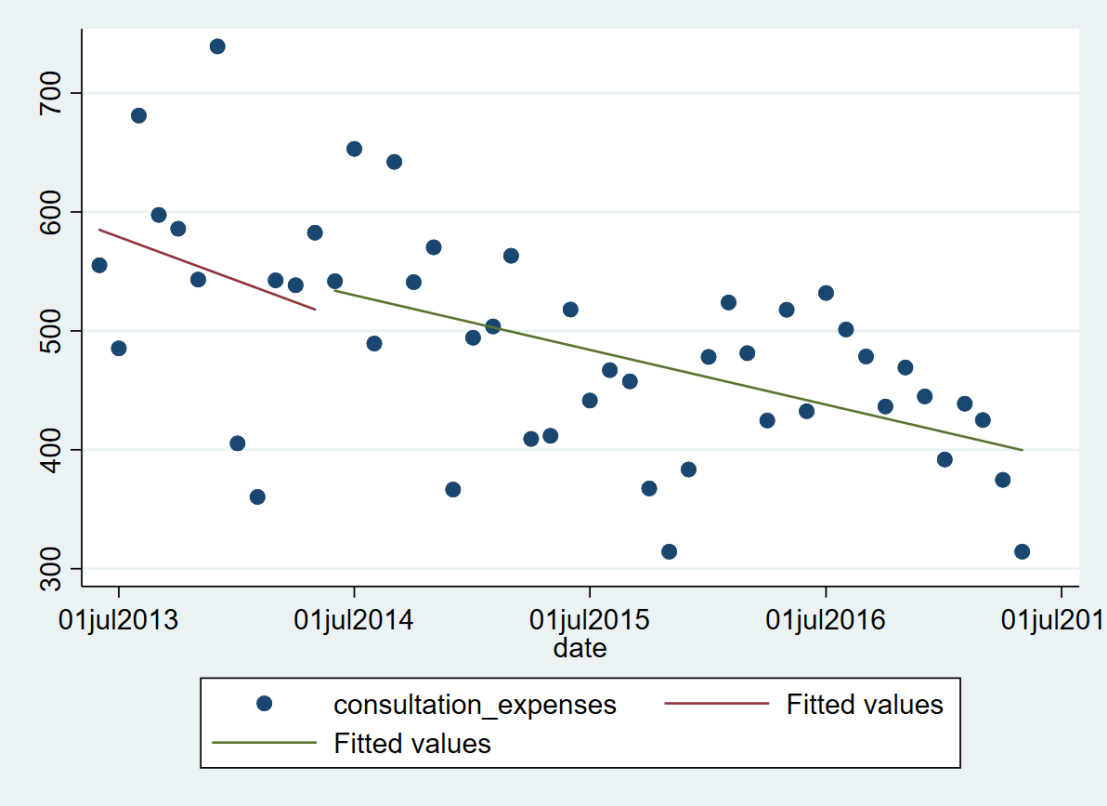

Figure 5-11 Linear regression graph of consultation expenses

Table 5-23 Linear regression results on consultation expenses

Variables	Estimated Parameter	Standard Deviation	P value
Intercept	590.54	48.35	<.0001
X^1	-6.02	6.57	0.3643
X^2	-6.89	63.14	0.9136
X^3	2.19	6.69	0.7453
R^2	0.3186		0.0007

X^1: slope prior to the intervention (Baseline trend)
X^2: change in the level immediately after the intervention (level change)
X^3: change in the slope from the pre-to-post intervention periods (trend change)

Diagnostic expenses

As shown in Figure 5-12, the fitted trend line showed the change in slope after the introduction of CP intervention. There was an increasing trend before CP intervention and a decreasing trend after intervention. The distribution of scatters is

similar with that of total hospitalization expenses and medication expenses. However, from the statistical point of view, all parameters of regression are not statistically significant, which indicates the effect is limited, see

Table 5-24.

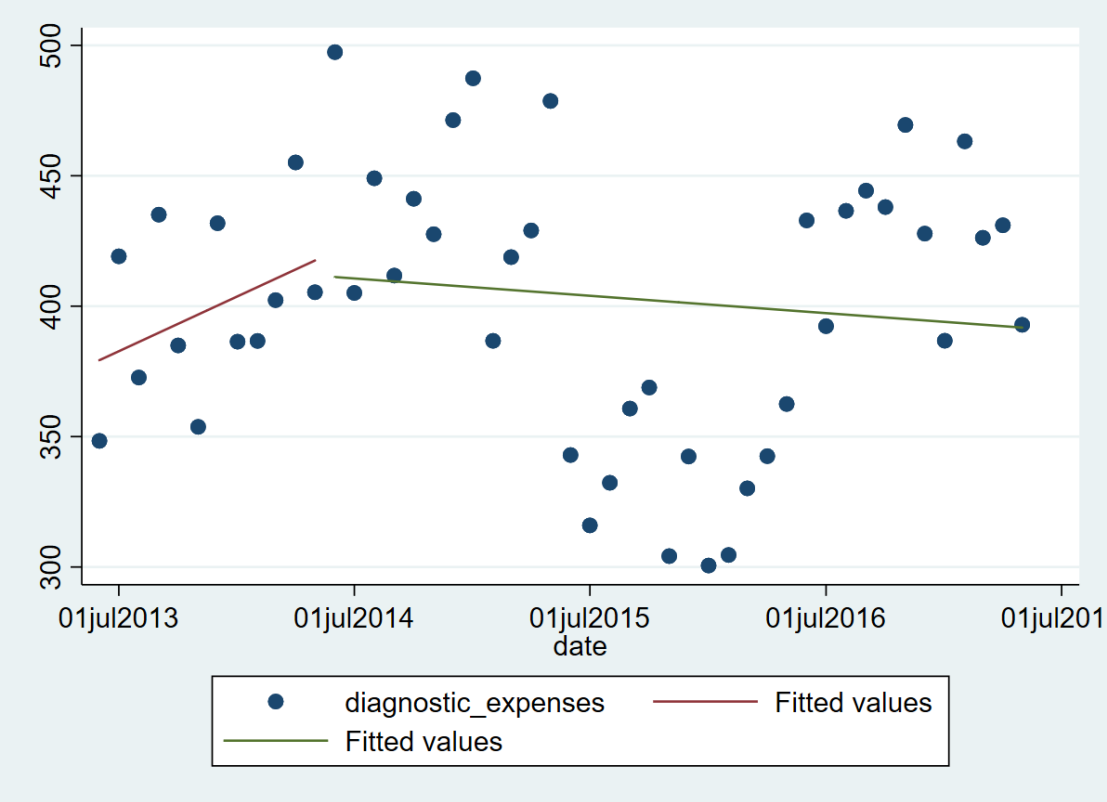

Figure 5-12 Linear regression graph of diagnostic expenses

Table 5-24 Linear regression simulation test result of diagnostic expenses

Variables	Estimated Parameter	Standard Deviation	P value
Intercept	375.77	32.06	<.0001
X^1	3.49	4.36	0.4271
X^2	42.66	41.87	0.3139
X^3	-4.05	4.44	0.3664
R^2	0.0247		0.7739

5.3.3. Markov Modeling of intervention

Clinical inputs

The clinical model inputs are transition probabilities between outpatient and inpatient status, and mortality rate.

Transition probabilities between states

To identify probabilities between different states, a keyword search was conducted in MEDLINE (09/2018) using the keywords “clinical pathway*”, “care pathway*”, “critical path*”, “care implementation*”, “cerebral infarction”, “stroke”, “economic evaluation”. The goal was to find population-based data that described the transition probabilities in CI patients at acute or stable stages. Of the 6 search results, one paper was screened in full. It was from China (Tu, 2016) which provided rehospitalization rate at population level. Rehospitalization rate was considered as probabilities from outpatient to inpatient in the model describing patients at stable stage.

Probabilities of inpatient to outpatient are directly calculated using data after the PSM (Table 5-8). For patients at acute stage, the discharge rates were calculated by day and considered as transition probabilities from inpatient to outpatient, the calculation equation is as follows:

$$\text{Daily discharge rate} = \frac{\text{Number of discharged patient in specific day}}{\text{Total number of inpatients}}$$

All patients are assumed to be discharged within one year when they are at stable stage. Transition probabilities can be found in Appendix C3.

Mortality rate

Chinese natural mortality data are available for males and females over the lifetime (Statistics, 2015). The general mortality rate was used as the natural mortality rate for outpatients in stable stage. Annual mortality rates from age of 60 and above were used in each cycle accordingly.

Daily mortality rates of inpatients at acute stage were calculated using the data from pilot hospital, calculation equation can be seen as below.

$$p = 1 - e^{-rt}$$

Probability p is a measure of likeliness that an event will occur (over a specified time period)

Rate r is number of events per unit time in a defined population (epidemiology)

Mortality rates of outpatients at acute stage for CP and non-CP arms were derived from literature (Chen, Gao, & Liu, 2017), see Table 5-25. Mortality rate of outpatients at stable stage for CP and non-CP arms were derived from China's Population and Employment Statistical Yearbook 2015 (Statistics 2015). The mortality rate of inpatients at both acute and stable stages were derived from real world data collected from the pilot site.

Table 5-25 Mortality rates used in two models

Stage	Intervention	State	Mortality rate	Source
Acute	CP	Outpatient	0.000453	(Chen et al., 2017)
		Inpatient	0.0000004056	Real-world data
	Non-CP	Outpatient	0.000453	(Chen et al., 2017)
		Inpatient	0.0000024389	Real-world data
Stable	CP	Outpatient	Appendix C4	(Chen et al., 2017; Statistics, 2015)
		Inpatient	0.0001480604	Real-world data
	Non-CP	Outpatient	Appendix C4	(Statistics, 2015)
		Inpatient	0.0008902087	Real-world data

Health related quality of life

Health related quality of life data (based on the EQ-5D-3L) for patients in the acute stage was directly collected from patients in the pilot hospital. Patients completed the questionnaire on the day of discharge. Utility data at admission stage was excluded due to data quality, primarily incompleteness of questionnaires at time of admission. Lack of utility data upon admission may lead to bias, which may cause the overestimate of the intervention effect. For the economic analysis, the Chinese EQ-5D-3L value set was applied to calculate the utility values (G. G. Liu et al., 2014).

One paper from the UK (Hunter et al., 2018) provided utility value of outpatients measured by Barthel Index at population level, see Table 5- 26.

Table 5- 26 Health state utility values after intervention

Intervention	State	Utility (Mean value)	Standard error	Source
CP	Outpatient	0.558	0.0156	(Hunter et al., 2018)
	Inpatient	0.4284	0.0504	Real-world data
Non-CP	Outpatient	0.558	0.0156	(Hunter et al., 2018)
	Inpatient	0.2500	0.0299	Real-world data

Cost inputs

Cost means the actual expenses charged by hospital. The cost inputs incurred in the outpatient state consist of medication costs, radiology expenses, laboratory test expenses and consultation costs. In the inpatient state, diagnostic expenses were introduced in inpatient cost beyond outpatient expenses. Only inpatient costs can be directly derived from HIS, detailed analysis of results can be found in section 5.3.1.1 (Table 5-8). For costs incurred in the outpatient state, expert consultation was conducted for data collection. In addition, the initial project investment, accounting for 10,000 YUAN, was also included. But the initial investment will be amortized over a longer time horizon.

All costs are converted to 2014 base year using the prices index from the National Bureau of Statistics (Statistics).

Outpatient costs

In the absence of cost data from either the pilot hospital or from published literatures, estimates of outpatient costs were based on expert consultation from pilot hospital. The clinicians were asked about their individual experiences and treatment practices refer to volume, frequency, and unit costs of prescription items. It is assumed that outpatient costs are equal between CP and Non-CP.

Drug costs

Data on drugs used by outpatients and the unit cost for each kind of drug were obtained from clinician consultation (see Table 5-27). Aspirin and Atorvastatin Calcium are two drugs used frequently by local physicians for CI patients after discharge. The combination of these two drugs could be an alternative option for some patients based on their symptoms. Total drug cost per cycle was calculated based on the proportion of patients allocated into various therapy utilization patterns,Table 5-28. Total drug cost for outpatient per year is ¥1,908.04.

Table 5-27 Cost of each drug for outpatients

Drug	**Units/pack**	**Dose（mg）/Unit**	**Cost/pack**	**Targeted mg/day**	**Cost/day**	**Cost/year**
Aspirin Enteric-coated	30	100	¥15.3	100	¥0.51	¥186.15
Atorvastatin Calcium	7	20	¥39.48	20	¥5.64	¥2058.60

Table 5-28 Cost of outpatients per year

Therapy of utilization	% of patients	Costs
Aspirin Enteric-coated+Atorvastatin Calcium	70.00	¥1571.33
Aspirin Enteric-coated	15.00	¥27.92
Atorvastatin Calcium	15.00	¥308.79
	Total cost	**¥1,908.04**

Medical resource use

Frequencies and the proportion of patients using medical resources in each cycle, such as consultation, laboratory test and radiology services are presented in Table 5-29. Total medical resource use for outpatient per cycle is ¥ 2,320.68.

Table 5-29 Medical resource use

		% of patients	Frequency per cycle
Consultation	Oncologist-junior	55%	12
	Oncologist-senior	45%	12
	Total costs		¥ 46.80

Laboratory test	Biochemistry	5.95%	4
	Blood test	60%	4
	Stool test	8%	2
	Urine test	40%	1
	Total costs		¥ 60.24
Radiology	Ultrasound	50%	1
	CT scan	50%	2
	MRI scan	33%	1
	Total costs		¥ 365.84
Total cost per cycle	¥ 2,320.68		
Total cost per day	¥ 6.36		

Unit costs for medical resource use were taken from pilot hospital and converted to 2014 prices using the data from National Bureau of Statistics(Statistics),see Table 5- 30.

Table 5- 30 Medical resource use unit costs

Cost item		
Consultation	Oncologist-junior	¥ 3.00
	Oncologist-senior	¥ 5.00
Laboratory test	Biochemistry	¥ 65.00
	Blood test	¥ 18.00
	Stool test	¥ 1.30
	Urine test	¥ 3.40
Radiology	Ultrasound	¥ 60.00
	CT scan	¥ 170.00
	MRI scan	¥ 320.00

Costs at acute stage (Inpatients)

Inpatient costs are calculated using data collected as part of the CP implementation from the pilot hospital (see section 5.3.1.1, Table 5-8). The total

average inpatient cost for CP managed patients is ¥4,447.79 and for Non-CP patients ¥4,400.85 (see Table 5- 31).

Table 5- 31 Break-down of costs for inpatients

	CP		Non-CP	
	Mean	Standard error	Mean	Standard error
Drug costs	¥191.14	46.08	¥206.40	68.38
Radiology costs	¥354.85	218.96	¥383.73	238.59
Laboratory test costs	¥666.32	245.28	¥750.12	341.57
Consultation costs	¥483.50	395.01	¥469.92	401.70
Diagnosis costs	¥392.70	172.54	¥400.96	222.36
Total costs	¥4,447.79	1287.62	¥4,400.85	1545.32

Validation

Face validity and peer review

The development of the model included in this report was undertaken with support from various stakeholders and experts; these included stroke specialists from the China National Clinical Research Center of Neurological Diseases and senior modelers from the China Health Economic Association. Feedback on model structure and input data was obtained through various rounds of consultation, dissertation review, national/international scientific conferences, and commentary from experts. Their inputs led to the development of a model that defined ‘acute’ and ‘stable stages’ following a CI disease management progress.

5.3.3.1. Cost-effectiveness analysis results

Base-case analysis

The base case analysis undertaken in two stages: cost-effectiveness estimates were generated for the acute and stable stages separately. An overall estimate of the incremental cost-effectiveness was then estimated (see section 4.4.4 for more detail on the methodology)

Cost-effectiveness results for acute stage:

The mean average hospitalization cost was ¥3,678.57 per patient in the intervention arm compared with ¥3,400.23 in the control arm, yielding a cost difference of ¥278.34 in favor of the Non-CP group instead of the CP group. CP treatment results in 0.031 QALY versus 0.028 QALY of Non-CP treatment, resulting in an intervention difference of 0.003 QALY. The incremental cost-effectiveness ratio was determined to be ¥103,450.45/QALY, which means that the administration of CP intervention resulted in an extra 1 QALY at an additional cost of ¥103,450.45(Table 5-32). As stated, the Shannxi GDP per capita in 2014 is ¥46,929.00. As recommended by Ochalek or Woods et al (Revill et al., 2015), if we set the threshold value as 1 times of 2014 Shannxi local GDP, equivalent to ¥46,929.00, the intervention strategy is not cost-effective compared to Non-CP treatment, because the ICER is much higher than the threshold value.

Table 5-32 Base-Case analysis of acute stage

Strategy	Costs	ΔCosts	QALYs	Δ QALYs	ICER
Non-CP group	¥3,400.23		0.028		
CP group	¥3,678.57	¥278.34	0.031	0.003	¥103,450.45/QALY

Cost-effectiveness results for stable stage:

The annual mean average outpatient cost was ¥42,365.38 per patients in the intervention arm compared with ¥32,223.84 on the control arm, yielding a cost difference of ¥10,141.54 in favor of the Non-CP group instead of the CP group. CP treatment results in 6.755 QALY versus 6.411 QALY of Non-CP treatment, resulting in an intervention difference of 0.344 QALY. The incremental cost-effectiveness ratio was estimated to be ¥29,497.55/QALY, which means the administration of CP intervention resulted in an extra of 1 QALY at an additional cost of ¥29,497.55 (Table 5-33). As stated, the Shannxi GDP per capita in 2014 is ¥46,929.00. If we set the threshold value as 1 times of 2014 Shannxi local GDP, equivalent to ¥46,929.00, the

intervention strategy is cost-effective compared to Non-CP treatment, because the ICER is lower than the threshold value.

Table 5-33 Base-Case analysis of stable stage

Strategy	Costs	ΔCosts	QALYs	Δ QALYs	ICER
Non-CP group	¥32,223.84		6.411		
CP group	¥42,365.38	¥10,141.54	6.755	0.344	¥29,497.55/QALY

Cost-effectiveness results overall:

The overall mean average cost was ¥46,043.94 per patient in the intervention arm compared with ¥35,624.06 in the control arm, yielding a cost difference of ¥10,419.88 in favor of the Non-CP group instead of the CP group. CP treatment results in 6.786 QALY versus 6.440 QALY of Non-CP treatment, resulting in an intervention difference of 0.347 QALY. The incremental cost-effectiveness ratio was estimated to be ¥30,071.79/QALY, which means the administration of CP intervention resulted in an extra of 1 QALY at an additional cost of ¥30,071.79 (Table 5-34). As stated, the Shannxi GDP per capita in 2014 is ¥46,929.00. As recommend by Ochalek or Woods et al (Revill et al., 2015), if we set the threshold value as 1 times of 2014 Shannxi local GDP, equivalent to ¥46,929.00, the intervention strategy is cost-effective compared to Non-CP treatment, because the ICER is lower than the threshold value.

Table 5-34 Base-Case analysis overall

Strategy	Costs	ΔCosts	QALYs	Δ QALYs	ICER
Non-CP group	¥35,624.06		6.440		
CP group	¥46,043.94	¥10,419.88	6.786	0.347	¥30,071.79/QALY

In the short run (acute stage), CP intervention of CI patients was not cost-effective, since the ICER value was higher than the pre-defined threshold value. However, the intervention of CP provided a better quality of life as indicated by higher QALYs. In the long run (acute stage), CP intervention of CI patients was cost-

effective, since the ICER value was lower than the pre-defined threshold value. In the both phases combined, CP intervention of CI patients was cost-effective, whose ICER was lower than the pre-defined threshold. In addition, the intervention of CP introduced the better quality of life as indicated by higher QALYs. To sum up, the impact of CP intervention was observed to be not cost-effective in short term (acute stage), but tending to be cost-effective in long term (acute and stable stage combined)

5.3.3.2. Sensitivity analysis

One-way sensitivity analysis

Results of one-way sensitivity analysis (OWSA) for combined case are presented in Figure 5-13. The top ten most influential parameters were identified by using OWSA, more details can be found in Figure 5-13.

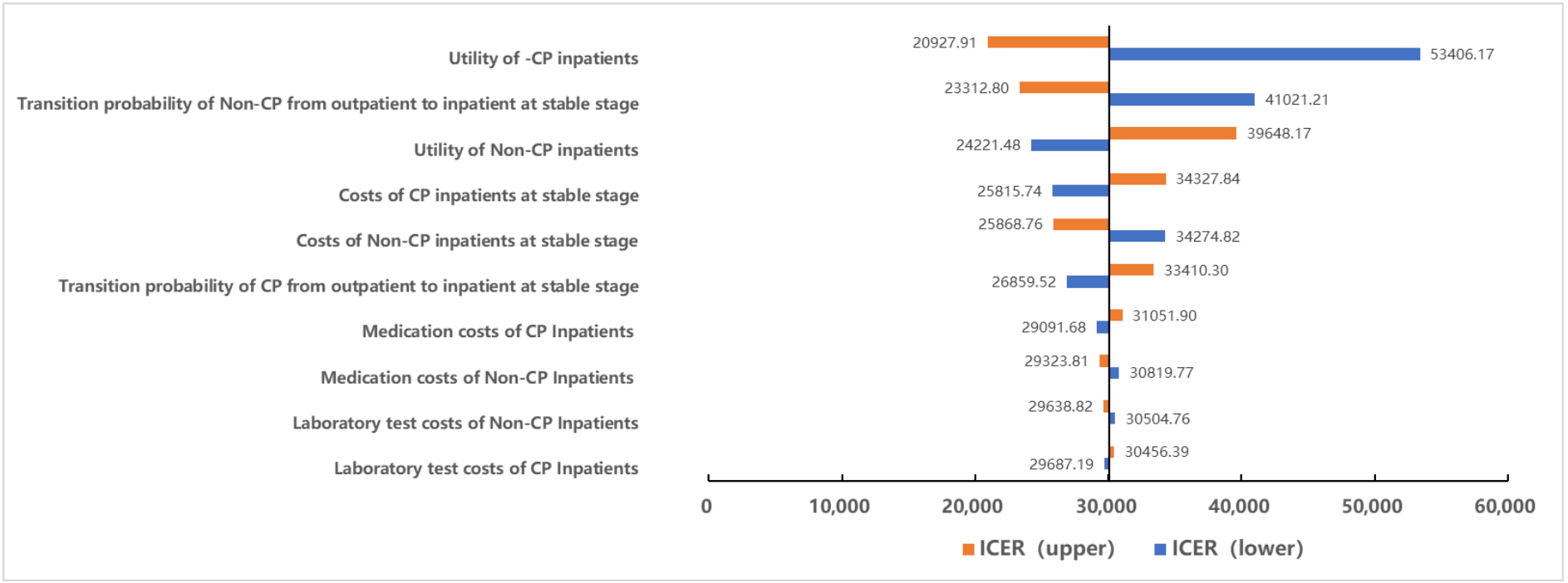

Figure 5-13 Tornado diagram (CP vs Non-CP)

Probabilistic sensitivity analysis (PSA)

The results of 1,000 PSA simulations were plotted on the CEP (Figure 5-14) and a CEAC was generated (Figure 5-15). Detailed distribution of parameters can be found in Appendix C5.

In the comparison with Non-CP, the average incremental costs were ¥10,401.01, and the average incremental QALYs were 0.353; this is consistent with the findings of the deterministic analysis of incremental costs and QALYs: ¥ 10,419.88 and 0.347, respectively. Almost all of the plots are located in the Northeast quadrant with results of higher cost and higher effectiveness compared with Non-CP. The proportion of simulations which was considered cost-effective at a threshold of ¥46,929 (2014 per capita GDP of Shannxi Province) per QALY was 88.90%.

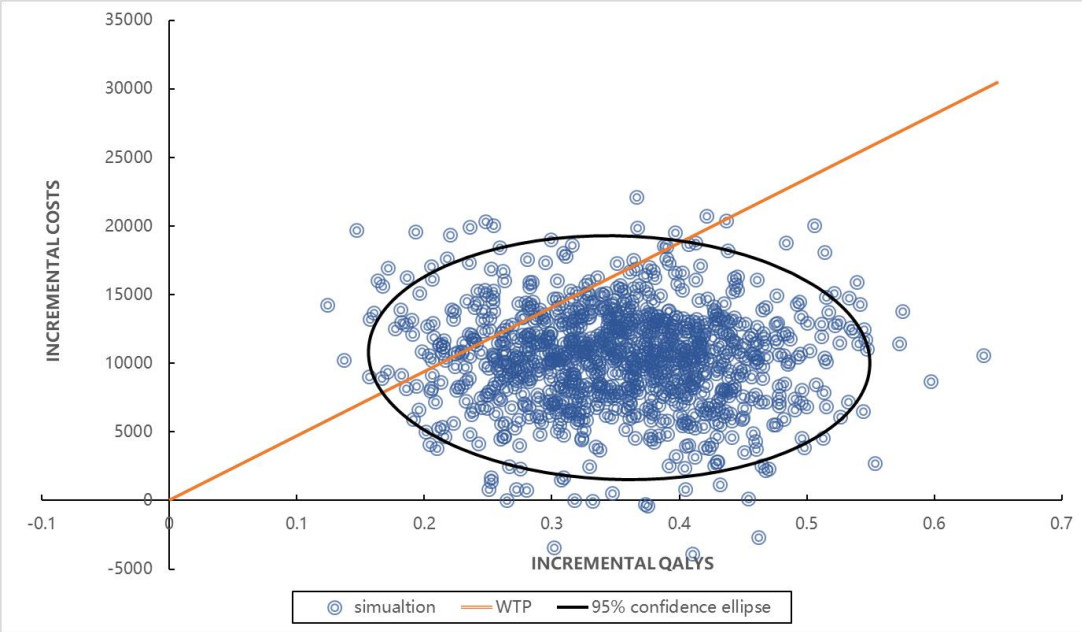

Figure 5-14 Cost-effectiveness plane (CP vs Non-CP)

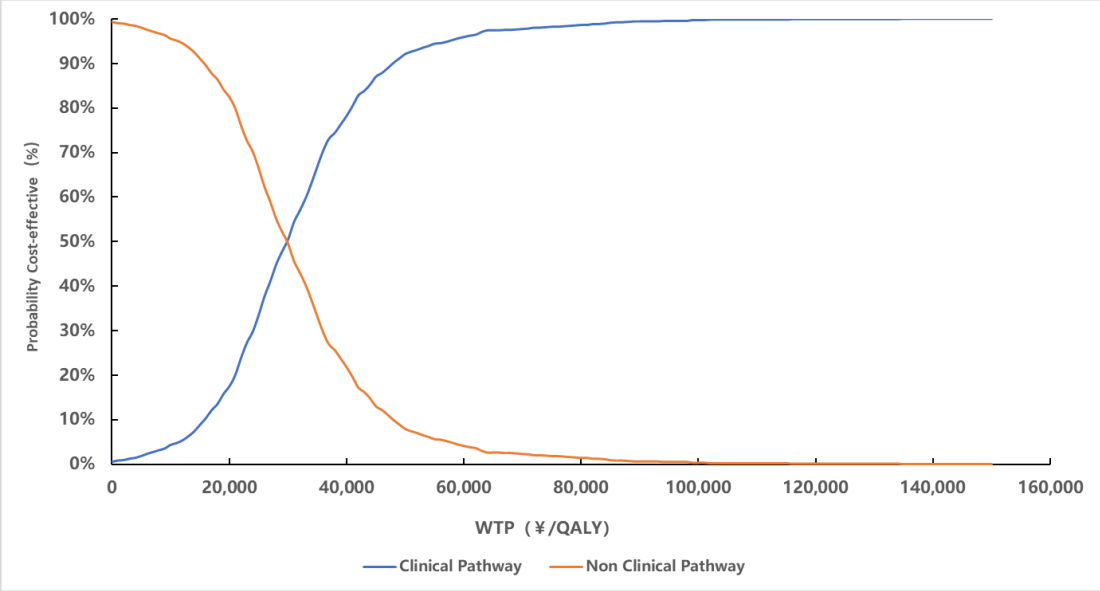

Figure 5-15 Cost-effectiveness acceptability curve (CP vs Non-CP)

Chapter 6 Discussion

Summary of Chapter

Translating research evidence into practice remains a persistent challenge because of diverse and idiosyncratic application settings. This chapter aims to outline interpretations of the analytical results, potential causal factors attributable to research findings, implications for future studies and the strengths and limitations of this impact evaluation study. The comments outlined in this chapter were generated after mapping a review of the literature and proposals by local practitioner and project staffs generated by site investigations. In line with the pre-defined study rationales, this discussion was seen as an additional way to understand CP effectiveness and facilitate scaling up CP intervention in China.

6.1. Interpretation of research findings

In term of the data analysis, we employed three major methodologies to examine the efficacy and cost-effectiveness of the intervention in a rural Chinese setting. The application of DID in support of PSM aims to explore the aggregated effectiveness of intervention through comparing subgroups, given balanced patient baseline characteristics. The application of ITS aims to explore the change in trend and intercept before and after acting on primary outcomes. The application of the Markov model aims to examine the cost-effectiveness of interventions covering both the hospitalization stage and the post-discharge stage.

In term of the research findings, DID in support of PSM indicates there is more likely a positive net effect attributed to CP intervention using the aggregated mean values; ITS results imply that effects of CP intervention on intercept and change in trend are limited. The coefficients of most regression models seem statistically

insignificant, but the intercept and trend change can be shown in the figures. The results of the Markov models in defining disease management show that CP intervention is cost effective combining the short and long-term models. The result of the short-term model indicates that the CP intervention is not cost-effective using one-time per capita GDP as a threshold, while the results of the long-term and combination models are cost effective.

Per analytical progress, there are some comments as follows:

6.1.1. Influence of incomplete data set

The quantitative study employed data extracted from the pilot hospital information system, focusing mainly on expense rather than clinical outcomes. Therefore, given the limitation of dataset records, the impact of intervention can only be interpreted by expenses data, LOS and utility value. In terms of the PSM analysis, the inclusion of covariates in estimation of propensity scores was limited, resulting in reduced accuracy in score matching. In term of the Markov models, the structure of the model was simplified into three disease management states rather than following the trajectory of the clinical outcome of disease progressions. In addition, some of input parameters in modeling were supported by literature and expert consultations rather than the recorded clinical data taken directly from pilot hospital information system.

6.1.2. Diluted effect of ITS analysis

The introduction of CP is a complex intervention affecting the entire population in the pilot site. Given the absence of a control hospital, the ITS comparison study used patient groups before and after intervention to assess the overall intervention impact.

Because of the mixture of treated and untreated patients, the effectiveness of CP intervention was diluted during the intervention period. Comparisons between

subgroups, such as “treatment before” versus “treatment after” and “control before” versus “control after,” were conducted to strengthen the exploration of intervention effectiveness. Study results of ITS focusing on subgroups as per above will be shared upon request.

6.1.3. Potential alternatives to optimize the ITS regression

As seen in ITS results, the values of R^2 referring to certain primary outcomes were relatively low, which means the regression simulation showed limited representation of scatter plots. The primary outcomes included total hospitalization expenses, medication expenses and diagnostic expenses. According to the illustration of the ITS scatter plot, there is a common pattern of change in the three primary outcomes mentioned before, after introduction of the CP. Therefore, the introduction of additional dummy variables in existing regression models could be used to provide a better fitting model, for example, the covariate of disease severity, or the period of time since the intervention.

6.1.4. Markov models covering short-term and long-term

In treatment of CI, the development of the Markov model should take consideration of both the acute stage and the stable stage. Building the Markov model was done with assistance from and in consultation with clinical experts. Given the limited variables in relation to disease prognosis, the disease states were defined in connection with type of medical services and disease progression. This design model is in line with a study conducted in the United Kingdom (Hunter et al., 2018). The cycle length of the acute model is one day, since the CP prescriptive items were allocated into days and the transition probabilities (inpatient to outpatient and inpatient mortality) can be accessed based on data collected from the pilot hospital. The time horizon of the acute model is 21 days, which is consistent with the maximum LOS required by CP. The

cycle length of the stable model is one year, as recommended by clinicians. Most of the parameters in the stable model, except inpatient mortality, are derived from literature rather than data from the pilot hospital. Considering lifetime disease management and Chinese life expectancy, the time horizon of the stable model is 20 years.

6.1.5. Implication of quality of life measurement

Using the EQ-5D-3L as a measurement questionnaire to evaluate patient quality of life has been widely accepted around the world and this study introduced it in the hospitalization stage to evaluate patient quality of life. Taking advantage of the Chinese utility value set, the quality of life measurement in this study is most likely representative of the preferences of the Chinese population. Detailed analysis focusing on each domain of EQ-5D-3L can be done in the future to accommodate the specific effectiveness of CP intervention in regards to mobility, self-care, normal activities, pain/discomfort, and anxiety/depression. However, the sensitivity of EQ-5D-3L to measure patients with certain, specific diseases raises controversy. Given the absence of a disease-specific measurement questionnaire for stroke patients in China, the generic measurement questionnaire is a practical choice to assist this impact evaluation study.

6.2. Practical causal factors supporting CP intervention

This section aims to outline the causal factors that come with the process of CP implementation, which can also be seen as approaches to ensure implementation success at the pilot site and hospital.

6.2.1. Motivation of CP intervention

According to the results of the literature review, we can see that the original motivation for the intervention is a key factor resulting of disparate levels of effectiveness in different studies. In this study, the CP intervention initiated in the pilot hospital, along the progression of healthcare reform nationwide in China, provides a solid and feasible macro environment for CP implementation. In a centralized country as China, political will is an important precondition and powerful motivator. Taking advantage of ongoing national healthcare reform, the intervention got good coordination from local healthcare authorities in the pilot county. This not only allowed local authorities to meet political requirements in local healthcare reform, but also allowed them to use CP intervention to clean-up and standardize behavior of local healthcare practitioners, for example, profit-seeking over-prescription of medications. Thus, CP was recognized as a useful tool for standardization of practice, which was particularly needed in rural hospitals in China.

6.2.2. Rising awareness of evidence-based medicine (EBM)

Over-prescription and under-prescription caused by physician behavior has been criticized as the biggest driver of unreasonable and fast-growing healthcare expenditures. But because of the asymmetric levels of information on the demand and supply sides of healthcare services, this difficulty was hard to understand for a long time in China. With the progression of healthcare reforms, awareness of EBM has strengthened and achieved a broad level of support among various stakeholders. In dealing with the fast-growing of local health expenditures, the medical insurance agency can control unreasonable expenditures using CP as a standardized guide and quality control indicator. Given the distrustful relationship between patients and physicians in rural hospitals in China, the clinical practitioners in county hospitals can

offer better healthcare services, improve clinical capacities in a way that patients will understand and respect. This also can reduce strong patient concerns about their hospital bills. In short, evidence-based CP can be seen a standard tool to balance the interests of various stakeholders.

6.2.3. Flexibility of CP content

In some literatures, the CP was sarcastically referred to by clinical practitioners as a "cooking menu" because of the conflict between CP-required standardized treatments and the complexity and peculiarities of the needs of individual patients. CP should be tailored in consideration of the treatment setting and practitioner capacity. In this study, using current clinical practices in the pilot hospital as the basis for CP content development, a consensus was reached using amendments to existing practices following comments from top national stroke experts. Therefore, CP was developed by both senior neurology physicians from tertiary hospitals and the clinical practitioners from the pilot county hospital. The bilateral engagement likely ensures the feasibility of CP mapping within the local hospital setting that doesn't vary far from treatment principles defined by national stroke experts. The feasibility and flexibility of CP content is important in achieving local clinical practitioner support, which in turn ensures their willingness to use CP. Frankly, the evolution progress of behavior change of clinicians was not easy. Initially, physicians would include "optional" factors consistent with previous practice, but this gradually died out. Gradually, CP became a useful tool for standardization of practice – something that was particularly needed in rural reginal county-level hospitals. In order to ensure the basic quality of service and improve physician adherence to CP, the detailed prescribed items were defined into mandatory and optional ones, according to their importance and specific needs of individual patients. In addition, in order to increase

the feasibility and inclusion rate of the CP, common complications and comorbidities were included. The sub-pathways do not intend to cure complications and morbidities, but accommodate and stabilize them within the treatment of CI. The finalization of proposed items was reviewed iteratively by local physicians and senior clinical consultants together based on their views of EBM and the practical capacities of local physicians. In addition, as a dynamic intervention, the CP has been optimized continuously to match the changing of local setting (for example, improved capacity of local physicians, or greater oversight on prescriptions) and interaction with other confounding factors, such as implementation of essential drug policies, etc. The ultimate goal of these efforts was to obtain physician recognitions and increase the flexibility of CP.

6.2.4. Supportive information system

CP management modules embedded into hospital information systems can improve working efficiency and change prescription behavior. In an environment in which all patient-oriented data can be tracked down, the information systems can also record prescription activities in a timely manner and facilitate the monitoring, evaluation and auditing of same. This can help support healthcare decision-making and the formation of a clinical, decision-supporting system based on the amount and quality of available data. It can bridge the gap between knowledge and practice and ensure that the right treatment can be offered to patients.

6.2.5. Capacity building for CP practitioners

Capacity building is a crucial factor, a precondition even, to ensure the success of project implementation in pilot hospitals. This intervention involved various types of medical staffs in the hospital who were not quite familiar with the content of CP, their role in a multi-disciplinary team (MDT), or with the working mechanisms at the

beginning of the intervention. Round after round of training workshops were offered with the aim of helping them understand the concept of evidence-based disease management, intervention objectives, rationales for prescriptive items and demonstration of practical skills in operating the information system. The workshops were delivered by project experts and local trainers involved in the design and development of earlier projects. Peer experience is highly effective in motivating, educating and influencing the understanding of those just learning CP.

6.2.6. Incentive mechanism

In order to motivate involvement by physicians and other medical staffs, hospital management introduced a series of supportive management measures to accommodate the implementation of CP. These included integrating medical staffs' salaries with the volume of patients managed by CP, setting bonus payments for outstanding physicians and nurses in CP, and implementing regulations on internal supervision and accountability. The incentive mechanism delivered a clear signal from hospital management and brings about positive reinforcement for practitioners who were coping with the changeover from the prescription-based system. Standardized clinical behaviors replaced unconscionable profits gained from inappropriate behavior.

6.2.7. Identification of confounding factors alongside the intervention

After introduction of CP intervention, changing patterns were observed in scatter plots of total hospitalization expenses, medication expenses and diagnostic expenses. There is an abrupt expense increase in the first five months after introducing CP to a pilot hospital, then a decreasing expenditure trend which reaches lowest rate one year after implementation. An increase in expenditures is observed again in the second year after intervention. Based on the consultation with local policy makers and practitioners, the following reasons were identified: 1) Reasonable and necessary

prescriptive services, not previously provided, had been included into the CP service package. This induced the abrupt increase in corresponding expenses shortly after introducing CP intervention. 2) A common prescribed and expensive drug, Edaravone, was delisted from the local medical insurance reimbursement scheme because of negative clinical evidence. This change caused a significant decrease in medication and total hospitalization expenses. Meanwhile, as the process of healthcare reform moves along, the awareness of EBM has been heavily strengthened and it's become mandatory for local health authorities. 3) Within one year of introducing of CP intervention, CP was optimized dynamically and more evidence-based prescriptive services and drugs were incorporated into the CP service package. Then an increasing trend was observed afterwards.

6.3. Implications for future studies

Based on the study findings and experiences gained from CP implementation at the pilot hospital, some academic and practical comments can be summarized to aid future studies and facilitate the dissemination of the study within the country and between China and other countries.

6.3.1. Payment reform

The CP intervention in this study did not integrate with payment reform. When we have seen payment reform in other parts of China, it has been a powerful tool to mitigate inappropriate behavior. Based on the lessons learned from other counties in China, it can be noted that there were spillover effects from the intervention to the control group due to the payment reform and evidence-based CP approach. Because the out-of-pocket payment of patients was reduced in taking celling case payment approach, but health status of CP patients improved significantly,, the CP management approach integrated with case payment is becoming more popular in

such areas (CNHDRC, 2015). If future studies can incorporate both payment reform and CP intervention, the general effectiveness of CP will be strengthened, for example, with stroke, replacing a fee-for-service scheme with a case payment scheme. With payment reform as part of the general scope of healthcare reform, local medical insurance agencies and healthcare providers can negotiate to set standards for case payment based on the actual cost of CP content. And the yearly adjustment mechanism can be set up to factor in inflation and clinical setting changes to form a dynamic and sustainable approach. To be sure, the case-based payment method should couple with quality indicators to control for quality of health outcomes. Ideally, the common comorbidities can also be considered for inclusion in the payment scheme. In addition, the case-based global budget is an alternative option for payment reform, in which a total annual budget is set to reach the aim of cost containment beyond cost controls for each, individual case.

6.3.2. Use of billing data

Billing data is the detailed, day-to-day record of expenses for all prescriptive items and resource consumed. In this study, only the general information presented by medical records was available, and not the billing data of prescribing behaviors by physicians and the services received by hospitalized patients, Taking advantage of billing data will allow later studies to observe prescription and service pattern changes. Such analysis can describe CP effectiveness in more detail and identify specific targets for CP optimization.

6.3.3. Key quality control indicators

Beyond the incentive measurements adopted in this study of CP intervention, key quality indicators should be created to monitor clinical practice performance. The original concept of CP development is to standardize clinical behavior. Following up

with a quality control indicator is a powerful way to monitor adherence to CP clinical practices and to correct unreasonable behaviors in a timely fashion. In addition, quality control indicators can be connected with medical insurance payouts to promote appropriate services for patients.

6.3.4. The integrated care pathway beyond acute stage treatment

The CP in this study focuses on the treatment protocol offered in the hospitalization stage. For stroke as a chronic disease, the CP concept can be extended into integrated care pathways covering prevention and rehabilitation. The adoption of integrated care pathways can be supported by township health centers and village clinics affiliated with the pilot county hospital. This provides an alternative option for improving the tiered medical services system in the current rural health setting, as proposed by national health authorities towards the lifelong management on chronic disease.

6.3.5. Initiate CP management of surgical disease

In the initiation stages of the introduction of CP management in county hospitals, the local practitioners can start with surgical procedures, such as acute simple appendicitis, elective surgery for benign gallbladder lesions, oblique inguinal hernia, and caesarean section. These kinds of conditions are diagnostically straightforward, rarely have comorbidities and have standardized treatments. CI is a complex disease with high possibility of comorbidities and variations in disease prognosis. With patient safety as the priority, patients were removed from CP management when very individual treatment needs arose. Initiating CP management on simpler surgeries can help practitioners get experience before heading to CP management of more difficult chronic diseases.

If complex diseases are chosen for CP management techniques, a balance must be struck between treatment principles and personalized issues.

6.3.6. Methodology recommendation

This study adopted three methodological approaches in this evaluation study: (1) DID in support of PSM, (2) ITS and (3) the Markov model. Choosing the right methodology depends on the data available in the project setting; there is no one method that is always right. If cost data and more clinical data is available, such as for stages and the severity of the disease, and on transitions in health status, the development of the Markov model seem more practical to simulate the trajectory of disease progress. (And estimation of propensity scores is more accurate in subsequent analysis.) If longitudinal data is available, the ITS analysis is recommended, given the removal of outlying data. If the control arm available, DID analysis is a straightforward and feasible approach for examining the effectiveness of intervention.

6.4. Strength of study

There are three strengths in terms of the study design and implications of the study results. One is the application of the PSM approach, the second is the introduction of the Markov model to explore the cost-effectiveness of CP intervention, and the third is the conclusion that the study created solid evidence to support healthcare decision-making in future iterations.

6.4.1. Application of PSM approach

The application of PSM aims to balance the variation of exposed, baseline factors towards improving the comparability between the treatment and control arms. Using the method of nearest neighbor matching, the age, gender, type of comorbidities, rather than number. of comorbidities, were matched on patients in the intervention and control arms. After the PSM, all the outlined indicators were not statistically different (using a P value of 0.05). The cost of matching is a reduction in sample size, but the refined, new sample increases the accuracy and reliability of research findings.

In the setting of real world and retrospective data, given the impossibility of RCT design, the PSM is a feasible and practical alternative solution in a quasi-experimental study. In the literature, the baseline data was not processed using the PSM normally used in observational studies. Thus, the conclusion of some similar studies outlines the significant difference in demographic baseline as a study limitation.

6.4.2. Building the Markov model

In the literature, there are fewer papers which focus on the cost-effectiveness of CP intervention. In this study, a group of complete Markov models was built to examine the cost-effectiveness of intervention impacts based on the practical treatment process within the Chinese rural healthcare system. In addition, most of the data input in the Markov model was collected from the pilot hospital so that reliable results could be obtained to benefit of local and national healthcare policy makers. The result of the Markov model provides visual and easily understood results to deliver to policy makers. Thus, the Markov model analysis was not only to address knowledge gaps in the literature regarding the effectiveness and cost-effectiveness of CP intervention for CI, but also to demonstrate the real-world impact of CP intervention in rural China and identify contextually appropriate solutions towards enabling continuous improvement.

6.4.3. Identification of causal factors attributed to CP intervention

The causal factors attributed to observed effects can be identified and explained better in a practical setting. In fact, the identification and understanding of causal factors is more important than observed results. In this discussion, the causal factors attributed to CP intervention included application setting, a supportive hospital information system, capacity building and incentive mechanisms. The identification of these

factors can facilitate the amending and improvement of CP intervention, aid CP dissemination on a larger scale and inform policy-making with evidence.

6.5. Limitations of study

6.5.1. Potential selection bias in patient grouping

In terms of grouping of patients before intervention, the local physicians, relying on the inclusion criteria defined by CP, reviewed patient health records to group patients before interventions into two subgroups, “before treatment” and “before control.” This sorting can facilitate DID analysis in the usual way, but it also introduces the possibility of subjectivity. In medical record reviews, the physician focuses on the treatment received by patients, but not patient baseline characteristics. The utilization of PSM can improve the accuracy and reliability of DID analytical results, as the baseline characteristics of patient data were balanced. But when applying the PSM in DID analyses, there is a concern about the sacrifice of sample size in the process of matching.

6.5.2. Absence of control subject

Another limitation in the analysis here is the lack of a control hospital. In ITS theory, a control subject better detect highlights the effectiveness of an intervention. In reality, all the Chinese hospitals, whether county- or upper-level, are experiencing different types of healthcare reform actions, e.g., payment reform, pricing reform, fiscal input reform and human resources reform. In this analysis, the neighboring pilot hospital in Hanbin county did not meet the requirements of a control subject, since their ongoing reform trials introduce confounding factors. This is why this study introduced the DID analysis on patients of Hanbin Hospital itself as an alternative solution.

In addition, data on individual patients' previous experience of CI would be important to collect in a future study, but not available for this study.

Chapter 7 Conclusions

A consistent conclusion in term of the impact of CP on health outcomes is difficult to generate using only a review of literature. But based on the impact evaluation of CI CP intervention in this study, the effectiveness of CP intervention in supporting of pre-defined primary outcomes in the pilot hospital is positive in comparison with the control group in the observation period. In terms of cost effectiveness, the CP intervention is not cost effective in the short run compared to non-CP practices. But in the long run, the CP intervention is a cost-effective intervention. Generally, the ICER of the combined Markov model is 30,071.79 YUAN/QALY, which is cost-effective under the threshold of one times local per capita GDP (46,929 YUAN).

In conclusion, the CP intervention is a practical solution to bring changes in standardized prescription behavior and contain unreasonable hospitalization expenses in rural China.

References

Association, A. S. (2016). About Stroke. Retrieved from https://www.stroke.org/en/about-stroke

Austin, P. C. (2011). An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res, 46*(3), 399-424. doi:10.1080/00273171.2011.568786

Baek, S., Park, S. H., Won, E., Yu, R. P., & Kim, H. J. (2015). Propensity Score Matching: A Conceptual Review for Radiology Researchers. *Korean Journal of Radiology, 16*(2), 286-296.

Barber, S. L., Michael, B., Henk, B., & Jin, M. (2014). The hospital of the future in China: China's reform of public hospitals and trends from industrialized countries. *Health Policy & Planning, 29*(3), 367-378.

Bettger, J. P., Li, Z., Xian, Y., Liu, L., Zhao, X., Li, H., . . . Wang, A. (2017). Assessment and provision of rehabilitation among patients hospitalized with acute ischemic stroke in China: Findings from the China National Stroke Registry II. *International Journal of Stroke Official Journal of the International Stroke Society, 12*(3), 254.

Briggs, A., Sculpher, M., & Claxton, K. (2006). *Decision modelling for health economic evaluation*: OUP Oxford.

Büchele, G., Och, B., Bolte, G., & Weiland, S. K. (2005). Single vs. double data entry. *Epidemiology, 16*(1), 130-131.

Cadilhac, D. a., Ibrahim, J., Pearce, D. C., Ogden, K. J., McNeill, J., Davis, S. M., & Donnan, G. a. (2004). Multicenter comparison of processes of care between Stroke Units and conventional care wards in Australia. *Stroke; a journal of cerebral circulation, 35*, 1035-1040. doi:10.1161/01.STR.0000125709.17337.5d

Cheah, J., . (2000). Development and implementation of a clinical pathway programme in an acute care general hospital in Singapore. *International Journal for Quality in Health Care Journal of the International Society for Quality in Health Care, 12*(5), 403-412.

Chen, W., Gao, R., & Liu, L. (2017). Report on China Cardiovascular Disease 2016. *Chinese Circulation Journal*.

Cheng, T. M. (2013). A pilot project using evidence-based clinical pathways and payment reform in China's rural hospitals shows early success. *Health Aff, 32*(5), 963-973.

CLINICAL, O. (2013). Clinical Pathways: multidisciplinary plans of best clinical practice.

CNHDRC. (2015). *Strengthening evidence-based policy making in support of universal healthcare*.

Commission, N. H. a. F. P. (2015). *Chinese Health Statistics Yearbook 2015*. Retrieved from Beijing:

Council, S. o. (2017). *The notice of deeping healthcare reform in "Thirteenth Five-Year " period by State of Council*. State of Council Retrieved from http://www.gov.cn/zhengce/content/2017-01/09/content_5158053.htm.

Craig, P., Cooper, C., Gunnell, D., Haw, S., Lawson, K., Macintyre, S., . . . Sutton, M. (2010). Using natural experiments to evaluate population health interventions. *College of Medical Veterinary and Life Sciences > School of Medicine*.

Crummer, M. B., & Carter, V., . (1993). Critical pathways--the pivotal tool. *Journal of Cardiovascular Nursing, 7*(4), 30-37.

D, Ö., A, E., & E, T. (2006). *Investigation of four different normality tests in terms of type 1 error rate and power under different distributions* (Vol. 36).

David, S., Anne, M., Inigo, P., & Lalit, K. (2002). Integrated care pathways and quality of life on a stroke rehabilitation unit. *Stroke; a journal of cerebral circulation, 33*(6), 1600-1604.

De Luca, A., Toni, D., Lauria, L., Sacchetti, M. L., Giorgi Rossi, P., Ferri, M., . . . Guasticchi, G. (2009). An emergency clinical pathway for stroke patients--results of a cluster randomised trial (isrctn41456865). *BMC health services research, 9*, 14. doi:10.1186/1472-6963-9-14

Dimick, J. B., & Ryan, A. M. (2014). Methods for evaluating changes in health care policy: the difference-in-differences approach. *JAMA, 312*(22), 2401-2402. doi:10.1001/jama.2014.16153

Donkor, E. S. (2018). Stroke in the 21(st) Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. *Stroke Res Treat, 2018*, 3238165. doi:10.1155/2018/3238165

Dorman, P. J., Waddell, F., Slattery, J., Dennis, M., & Sandercock, P. (1997). Is the EuroQol a valid measure of health-related quality of life after stroke? *Stroke, 28*(10), 1876-1882. doi:10.1161/01.str.28.10.1876

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). *Methods for the economic evaluation of health care programmes*: Oxford university press.

Drury, P., Levi, C., D'Este, C., McElduff, P., McInnes, E., Hardy, J., . . . Middleton, S. (2014). Quality in Acute Stroke Care (QASC): process evaluation of an intervention to improve the management of fever, hyperglycemia, and swallowing dysfunction following acute stroke. *International journal of stroke : official journal of the International Stroke Society, 9*, 766-776. doi:10.1111/ijs.12202

Dykes, P. C. (1997). *Psychiatric Clinical Pathways: An Interdisciplinary Approac*: Springer.

Evers, S. M. A. A., Struijs, J. N., Ament, A. J. H. A., Genugten, M. L. L., Van, Jager, J. H. C., & Bos, G. A. M., Van Den. (2004). International comparison of stroke cost studies. *Stroke, 35*(5), 1209-1215.

Fagerberg, B., Claesson, L., Gosman-Hedstrom, G., Blomstrand, C., Gosman-Hedström, G., & Blomstrand, C. (2000). Effect of acute stroke unit care integrated with care continuum versus conventional treatment: A randomized 1-year study of elderly patients: the Goteborg 70+ Stroke Study. *Stroke, 31*, 2578-2584. doi:10.1161/01.STR.31.11.2578

Fagerberg, B., Claesson, L., Gosmanhedström, G., & Blomstrand, C. (2000). Effect of acute stroke unit care integrated with care continuum versus conventional treatment: A randomized 1-year study of elderly patients: the Göteborg 70+ Stroke Study. *Stroke; a journal of cerebral circulation, 31*(11), 2578-2584.

Ferri, C. P., Schoenborn, C., Kalra, L., Acosta, D., Guerra, M., Huang, Y., . . . Sosa, A. L. (2011). Prevalence of stroke and related burden among older people living in Latin America, India and China. *Journal of Neurology Neurosurgery & Psychiatry, 82*(10), 1074-1082.

Fretheim, A., & Tomic, O. (2015). Statistical process control and interrupted time series: a golden opportunity for impact evaluation in quality improvement. *BMJ Qual Saf, 24*(12), 748-752. doi:10.1136/bmjqs-2014-003756

Fu, H., Li, L., Li, M., Yang, C., & Hsiao, W. (2017). An evaluation of systemic reforms of public hospitals: the Sanming model in China. *Health Policy &*

Planning, 32(8), 1135.
Gao, Y., Jiang, B., Sun, H., Ru, X., Sun, D., Wang, L., . . . Wang, Y. The burden of stroke in China: Results from a nationwide population-based epidemiological survey. *PLoS One*.
Group, W. B. (2019a). GDP growth (annual %). *World Bank national accounts data, and OECD National Accounts data files.* Retrieved from https://data.worldbank.org/indicator/NY.GDP.MKTP.KD.ZG
Group, W. B. (2019b). Population ages 65 and above (% of total population). *World Bank staff estimates based on age distributions of United Nations Population Division's World Population Prospects.* Retrieved from https://data.worldbank.org/indicator/NY.GDP.MKTP.KD.ZG?locations=CN
Hanna, E., ., Schultz, S., ., Doctor, D., ., Vural, E., ., Stern, S., ., & Suen, J., . (1999). Development and implementation of a clinical pathway for patients undergoing total laryngectomy: impact on cost and quality of care. *Arch Otolaryngol Head Neck Surg, 125*(11), 1247-1251.
Health, N. I. o. (2019). Stroke, also known as cerebrovascular Accident.
Higgins, J. P., & Green, S. (2008). *Cochrane Handbook for Systematic Reviews of Interventions*.
Hipp, R., Abel, E., & Weber, R. J. (2016). A Primer on Clinical Pathways. *Hosp Pharm, 51*(5), 416-421.
Hoffman, K. (2019). Process of care measures and infection control. Retrieved from https://www.infectiousdiseaseadvisor.com/home/decision-support-in-medicine/hospital-infection-control/process-of-care-measures-and-infection-control/
Hunter, R. M., Fulop, N. J., Boaden, R. J., Mckevitt, C., Perry, C., Ramsay, A. I. G., . . . Wolfe, C. D. A. (2018). The potential role of cost-utility analysis in the decision to implement major system change in acute stroke services in metropolitan areas in England. *Health Research Policy & Systems, 16*.
Isozaki, L. F. F., & Fahndrick, J. (1998). Clinical Pathways—A Perioperative Application. *Aorn Journal*.
Jacavone, J. B., Daniels, R. D., & Tyner, I. (1999). CNS facilitation of a cardiac surgery clinical pathway program. *Clinical Nurse Specialist Cns, 13*(3), 126-132.
Jamal, S. A., Vandermeer, B., Raggi, P., Mendelssohn, D. C., Chatterley, T., Dorgan, M., . . . Tsuyuki, R. T. (2013). Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet, 382*(9900), 1268-1277.
Jiang, Y., Yang, X., Li, Z., Pan, Y., Wang, Y., Wang, Y., . . . Wang, C. (2017). Persistence of secondary prevention medication and related factors for acute ischemic stroke and transient ischemic attack in China. *Neurological Research, 39*(6), 1.
Kontopantelis, E., Doran, T., Springate, D. A., Buchan, I., & Reeves, D. (2015). Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ, 350*, h2750-h2750. doi:10.1136/bmj.h2750
Kwan, J. (2007). Care pathways for acute stroke care and stroke rehabilitation: from theory to evidence. *Journal of Clinical Neuroscience, 14*(3), 189-200.
Kwan, J., & Sandercock, P. (2002). In-hospital care pathways for stroke. *Cochrane Database of Systematic Reviews, 34*(2), 587-588.

Lagarde, M. (2012). How to do (or not to do)...assessing the impact of a policy change with routine longitudinal data. *Health Policy and Planning, 27*, 76-83. doi:10.1093/heapol/czr004

Lan, X., Zhou, Z., Si, Y., Shen, C., Fan, X., Chen, G., . . . Chen, X. (2018). Assessing the effects of the percentage of chronic disease in households on health payment-induced poverty in Shaanxi Province, China. *BMC Health Services Research, 18*(1), 871.

Lancet, T. (2018). Stroke. Retrieved from https://www.thelancet.com/series/stroke

Lang, Z., Ling, X., Ye, J., Sun, S., Zhang, Y., Burstrom, K., & Chen, J. (2018). Time Trade-Off Value Set for EQ-5D-3L Based on a Nationally Representative Chinese Population Survey ☆. *Value in Health, 21*(11), S1098301518316735-.

Li, L., & Fu, H. (2017). China's health care system reform: Progress and prospects. *International Journal of Health Planning & Management, 32*(11).

Li, Y., Xu, J., Wang, F., Wang, B., & Lu, Z. (2012). Overprescribing In China, Driven By Financial Incentives, Results In Very High Use Of Antibiotics, Injections, And Corticosteroids. *Health Aff, 31*(5), 1075-1082.

Li, Z., Jiang, Y., Li, H., Xian, Y., & Wang, Y. (2019). China's response to the rising stroke burden. *Bmj, 364*, l879. doi:10.1136/bmj.l879

Li, Z., Wang, C., Zhao, X., Liu, L., Wang, C., Hao, L., . . . Yang, Q. (2016). Substantial Progress Yet Significant Opportunity for Improvement in Stroke Care in China. *Stroke, 47*(11), 2843-2849.

Liping, L., David, W., Wong, K. S. L., & Yongjun, W. (2011). Stroke and stroke care in China: huge burden, significant workload, and a national priority. *Stroke; a journal of cerebral circulation, 42*(12), 3651-3654.

Liu, G., Hu, S., & Wu, J. (2011). China Pharmacoeconomics Evaluation Guideline. *Pharmacoeconomics of China 3*, 6-48.

Liu, G. G., Wu, H., Li, M., Chen, G., & Nan, L. (2014). Chinese Time Trade-Off Values for EQ-5D Health States. *Value in Health, 17*(5), 597-604.

Liu, T., & Jin, S. (2009). The impact analysis of increasing mediacal expenses attributed to technology advancement. *Information of Economics and Law*(5), 42-46.

Long, Q., Xu, L., Bekedam, H., & Tang, S. (2013). Changes in health expenditures in China in 2000s: has the health system reform improved affordability. *International Journal for Equity in Health, 12*(1), 40-40.

Luo, N., Liu, G., Li, M., Guan, H., Jin, X., & Rand-Hendriksen, K. (2017). Estimating an EQ-5D-5L Value Set for China. *Value Health, 20*(4), 662-669. doi:10.1016/j.jval.2016.11.016

Mabrey, J. D., Toohey, J. S., Armstrong, D. A., Lavery, L., ., & Wammack, L. A. (1997). Clinical pathway management of total knee arthroplasty. *Clin Orthop Relat Res, 345*(345), 125-133.

Mahoney, F. I., & Barthel, D. W. (1965). FUNCTIONAL EVALUATION: THE BARTHEL INDEX. *Maryland State Medical Journal, 14*(14), 61-65.

Martínez-Sánchez, P., Fuentes, B., Medina-Báez, J., Grande, M., Llorente, C., Parrilla, P., . . . Olguín, C. (2010). Development of an acute stroke care pathway in a hospital with stroke unit. *Neurología, 25*(1), 17-26.

Matthias, S., Damir, P., Alexandra, B., Steckel, D. A., Stephan, V. K., Markus, H. S., & Helmuth, S. (2003). Internal carotid artery angle of origin: a novel risk factor for early carotid atherosclerosis. *Stroke; a journal of cerebral circulation, 34*(4), 950-955.

Maxey, C. (1997). A case map reduces time to administration of thrombolytic therapy

in patients experiencing an acute myocardial infarction. *Nursing Case Management Managing the Process of Patient Care, 2*(5), 229.
Medicine, T. C. f. E.-B. (2019). Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). Retrieved from https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
Meng, Q., Xu, L., Zhang, Y., Qian, J., Cai, M., Xin, Y., . . . Barber, S. L. (2012). Trends in access to health services and financial protection in China between 2003 and 2011: a cross-sectional study. *Lancet, 379*(9818), 805-814.
Middleton, S., Mcelduff, P., Ward, J., Grimshaw, J. M., Dale, S., D'Este, C., . . . Quinn, C. (2011). Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet, 378*(9804), 1699-1706.
Moher, D. (2010). Corrigendum to: Preferred Reporting Items For Systematic Reviews And Meta-Analyses: The PRISMA Statement International Journal of Surgery 2010; 8: 336-341. *International Journal of Surgery, 8*(8), 658-658.
Morris, S., Hunter, R. M., Ramsay, A. I., Boaden, R., McKevitt, C., Perry, C., . . . Fulop, N. J. (2014). Impact of centralising acute stroke services in English metropolitan areas on mortality and length of hospital stay: difference-in-differences analysis. *BMJ, 349*, g4757. doi:10.1136/bmj.g4757
NHC. (2009). Opinions of the CPC Central Committee and the State Council on Deepening the Health Care System Reform. Retrieved from http://www.doc88.com/p-1572294499113.html
NHC. (2018). *China health and family planning statistics yearbook 2018*: Peking Union Medical College Press.
Panella, M., Marchisio, S., Brambilla, R., Vanhaecht, K., & Di Stanislao, F. (2012). A cluster randomized trial to assess the effect of clinical pathways for patients with stroke: results of the clinical pathways for effective and appropriate care study. *BMC Medicine, 10*, 71. doi:10.1186/1741-7015-10-71
Pickard, A. S., Johnson, J. A., & Feeny, D. H. (2005). Responsiveness of generic health-related quality of life measures in stroke. *Quality of Life Research, 14*(1), 207-219.
Policies, A. P. O. o. H. S. a. (2015). *People's Republic of China health system review*.
Powers, W. J., Rabinstein, A. A., Ackerson, T., Adeoye, O. M., Bambakidis, N. C., Becker, K., . . . Hoh, B. (2018). 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Journal of Vascular Surgery, 67*(6), 1934-.
Prevention, C. f. D. C. a. (2019). Stroke.
Ramsay, C. R., Matowe, L., Grilli, R., Grimshaw, J. M., & Thomas, R. E. (2003). Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. *Int J Technol Assess Health Care, 19*(4), 613-623.
Revill, P., Ochalek, J., Lomas, J., Nakamura, R., Woods, B., Rollinger, A., . . . Claxton, K. (2015). Cost-effectiveness thresholds: guiding health care spending for population health improvement. *A report by the Centre for Health Economics, University of York, for the International Decision Support Initiative (iDSI). Centre for Health Economics, University of York.*
Reynolds, L., & Mckee, M. (2012). Serve the people or close the sale? Profit-driven overuse of injections and infusions in China's market-based healthcare system.

International Journal of Health Planning & Management, 26(4), 449-470.
Ringel, S. P., & Hughes, R. L. (1996). Evidence-Based Medicine, Critical Pathways, Practice Guidelines, and Managed Care: Reflections on the Prevention and Care of Stroke. *Archives of Neurology, 53*(9), 867.
Rosenbaum, P. R., & Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. *Biometrika, 70*, 41-55. doi:10.1093/biomet/70.1.41
Rotter, T., Kinsman, L., James, E., Machotta, A., Gothe, H., Willis, J., . . . Kugler, J. (2011). Clinical pathways: effects on professional practice, patient outcomes, length of stay and hospital costs. *International Journal of Evidence-Based Healthcare, 9*(2), 191-192.
Service, C. R. (2019). *China's Economic Rise: History, Trends, Challenges, and Implications for the United States*.
Silke, W., Panagiotis, K., Anton, H., Isabel, K., Martin, L., Thomas, S., . . . Helmut, S. (2012). Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurology, 11*(5), 397-404.
Sonnenberg, F. A., & Beck, J. R. (1993). Markov models in medical decision making: a practical guide. *Med Decis Making, 13*(4), 322-338. doi:10.1177/0272989X9301300409
Statistics, N. B. o. *China Statistical Yearbook 2014-2018*: China Statistics Press.
Statistics, N. B. o. (2015). *China population and employment statical yearbook 2015*: China Statistics Press.
Sulch, D., ., Perez, I., ., Melbourn, A., ., & Kalra, L., . (2000). Randomized controlled trial of integrated (managed) care pathway for stroke rehabilitation. *Stroke, 31*(8), 1929.
Sulch, D., Evans, A., Melbourn, A., & Kalra, L. (2002). Does an integrated care pathway improve processes of care in stroke rehabilitation? A randomized controlled trial. *Age and Ageing, 31*, 175-179. doi:10.1093/ageing/31.3.175
Sulch, D., Melbourn, A., Perez, I., & Kalra, L. (2002). Integrated care pathways and quality of life on a stroke rehabilitation unit. *Stroke, 33*, 1600-1604. doi:10.1161/01.STR.0000017144.04043.87
Sulch, D., Perez, I., Melbourn, A., & Kalra, L. (2000). Randomized controlled trial of integrated (managed) care pathway for stroke rehabilitation. *Stroke; a journal of cerebral circulation, 31*, 1929-1934. doi:10.1161/01.STR.31.8.1929
Torp, C. R., Vinkler, S., Pedersen, K. D., Hansen, F. R., Jørgensen, T., & Olsen, J. (2006). Model of hospital-supported discharge after stroke. *Stroke, 37*, 1514-1520. doi:10.1161/01.STR.0000221793.81260.ed
Tu, X. (2016). Epidemiological studies of acute ischemic stroke. *Chin J Clin Neurosci, 5*(24), 594-599.
Vanhaecht, K., De Witte, K., Depreitere, R., & Sermeus, W. (2006). Clinical pathway audit tools: a systematic review. *J Nurs Manag, 14*(7), 529-537. doi:10.1111/j.1365-2934.2006.00705.x
Vanhaecht, K., Ovretveit, J., Elliott, M. J., Sermeus, W., Ellershaw, J., & Panella, M. (2012). Have we drawn the wrong conclusions about the value of care pathways? Is a Cochrane review appropriate? *Evaluation & the Health Professions, 35*(1), 28-42.
Wagner, A. K., Soumerai, S. B., Zhang, F., & Ross-Degnan, D. (2002). Segmented regression analysis of interrupted time series studies in medication use research. *Journal of Clinical Pharmacy and Therapeutics, 27*, 299-309.

doi:10.1046/j.1365-2710.2002.00430.x
Walter, S., Kostopoulos, P., Haass, A., Keller, I., Lesmeister, M., Schlechtriemen, T., . . . Fassbender, K. (2012). Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: A randomised controlled trial. *The Lancet Neurology, 11*, 397-404. doi:10.1016/S1474-4422(12)70057-1
Wang, H., Gusmano, M. K., & Cao, Q. (2011). An evaluation of the policy on community health organizations in China: will the priority of new healthcare reform in China be a success? *Health Policy, 99*(1), 37-43.
Wang, L., Wang, J., & Peng, B. (2015). China Stroke Prevention and Treatment Report (2015) (Vol. 14, pp. 217): $2017.
Wang, W., Jiang, B., Sun, H., Ru, X., Sun, D., Wang, L., . . . Wang, Y. (2017). Prevalence, Incidence and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480,687 Adults. *Circulation, 135*(8), 759.
Wang, Y. L., Wu, D., Liao, X., Zhang, W., Zhao, X., & Wang, Y. J. (2007). Burden of stroke in China. *International Journal of Stroke, 2*(3), 211-213.
Wardlaw, J. M., Seymour, J., Cairns, J., Keir, S., Lewis, S., & Sandercock, P. (2004). Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke; a journal of cerebral circulation, 35*(11), 2477-2483.
Website, C. G. (2018). The subsidy of national basic public health service has reached to 55 YUAN in 2018. Retrieved from https://finance.sina.com.cn/roll/2018-07-26/doc-ihfvkitx2215170.shtml
Weingarten, S., . (2001). Critical pathways: what do you do when they do not seem to work? *American Journal of Medicine, 110*(3), 224-225.
WHO. (2011). *The World Medicines Situation Report, 2011*. Retrieved from https://www.who.int/medicines/areas/policy/world_medicines_situation/wms_intro/en/
WIKIPEDIA. (2019a). Cerebral Infarction.
Wikipedia. (2019b). Clinical pathway. Retrieved from https://en.wikipedia.org/wiki/Clinical_pathway
Wikipedia. (2019c). Kolmogorov–Smirnov test.
Wing, C., Simon, K., & Bello-Gomez, R. A. (2018). Designing Difference in Difference Studies: Best Practices for Public Health Policy Research. *Annu Rev Public Health, 39*, 453-469. doi:10.1146/annurev-publhealth-040617-013507
Wu, X., Zhu, B., Fu, L., Wang, H., Zhou, B., Zou, S., & Shi, J. (2013). Prevalence, incidence, and mortality of stroke in the chinese island populations: a systematic review. *PLoS One, 8*(11), e78629.
Xinhua. New action plan highlights health knowledge among primary, secondary school students. *CHINADAILY*. Retrieved from http://www.chinadaily.com.cn/a/201907/15/WS5d2c8f73a3105895c2e7d8ba.html
Y, W. (2012). *The implementation of clinical path management to promote healthcare quality improvement and efficiency*: Guide to Chinese Medicine.
Yip, C. M., Hsiao, W., Meng, Q., Chen, W., & Sun, X. (2010). Realignment of incentives for health-care providers in China. *Lancet, 375*(9720), 1120-1130.
Yip, W. C., Hsiao, W. C., Chen, W., Hu, S., Ma, J., & Maynard, A. (2012). Early appraisal of China's huge and complex health-care reforms. *Lancet, 379*(9818), 833-842.

Yunhua, H., Shihong, T., Min, S., Yuanjian, Z., Zhiyu, N., & Shujuan, Y. (2015). Association between matrix metalloproteinase gene polymorphisms and development of ischemic stroke. *International Journal of Clinical & Experimental Pathology, 8*(9), 11647-11652.

Zhang, H., Hu, H., Wu, C., Yu, H., & Dong, H. (2015). Impact of China's Public Hospital Reform on Healthcare Expenditures and Utilization: A Case Study in ZJ Province. *PLoS One, 10*(11), e0143130.

Zhang, L.-F., Yang, J., Hong, Z., Yuan, G.-G., Zhou, B.-F., Zhao, L.-C., . . . Wu, Y.-F. (2003). Proportion of different subtypes of stroke in China. *Stroke, 34*(9), 2091-2096.

zhang, S., & wu, J. (2016). *Diagnosis and treatment of complications of cerebral infarction*: Xiamen University Press.

Zhu, K., Zhang, X., Yuan, S., & Tian, M. (2016). Evolution, Achievements, and Challenges for New Cooperative Medical Schemes in Rural China. *Scientific Research*, 1564-1583.

ZX. (2019). China issues new documents to implement Healthy China initiative. *Xinhua*. Retrieved from http://www.xinhuanet.com/english/2019-07/15/c_138229290.htm

Appendix A

A1: General principles of clinical pathway

脑梗死临床路径

Clinical pathway of cerebral infarction

一、脑梗死临床路径标准住院流程

1. Standard inpatient care pathway of cerebral infarction

（一）适用对象。

(1) Indications

第一诊断为脑梗死(ICD-l0:I63)。

Primary diagnosis : cerebral infarction (ICD-10：I63).

（二）诊断依据。

(2) Diagnosis

根据《临床诊疗指南-神经病学分册》(中华医学会编著，人民卫生出版社)。

Diagnosis should be made on the basis of the China guideline for Neurologic Diseases (Compiled by the Chinese Medical Association and published by the People's Medical Publishing House)

1.临床表现:急性起病，出现局灶症状和体征，伴或不伴意识障碍。

i. Clinical manifestations: acute onset, focal neurologic signs or symptoms along with headache and/or dysfunction of consciousness;

2.头颅 CT 证实颅内无出血改变。

ii. No hemorrhage confirmed with brain scan.

（三）选择治疗方案。

(3) Treatment options and basis

1.整体治疗:

i. General treatment:

（1）卧床休息，维持生命体征和内环境稳定，预防感染等并发症；

a) Bed rest, stabilize vital signs and clinical status, prevent and treat infection

（2）维持呼吸道通畅，鼻导管吸氧；

b) Preserve the fluent respiratory tract, Nasal cannula oxygen

（3）不能经口喂食者给予鼻饲，以维持机体营养需要，避免吸入性肺炎；

c) Patients who can not be fed orally should have nasal feeding to maintain the nutrition, aspiration pneumonia should be avoided.

（4）控制血压；

d) Control blood pressure

（5）降低颅内压。存在颅内压升高的征象时，采取降颅压措施，药物可选用 20%甘露醇，严重时可考虑去骨瓣减压；

e) Decreasing intracranial pressure: when patients manifest increased intracranial pressure, lowering the pressure is recommended, and 20% mannitol is the optional medicine. If patients have severe conditions, decompressive craniectomy is recommended.

（6）控制体温在正常水平，38℃以上应给予物理和药物降温；

f) Maintain the temperature at the normal level, physical and drug cooling is recommended if patients' temperature is above 38℃.

（7）防治应激性溃疡；

g) Prevent and treat stress ulcer

（8）早期康复治疗。

h) Early rehabilitation care

2.特殊治疗：

ii. Special treatments:

（1）溶栓治疗（发病 3-6 小时之内）；

a) Thrombolytic therapy (within 3-6 hours after the onset)

（2）抗凝治疗；

b) Anticoagulation therapy

（3）抗血小板治疗；

c) Antiplatelet therapy

（4）降纤治疗；

d) Defibrate therapy

（5）神经保护治疗；

e) Neuroprotective therapy

（6）中药治疗。

f) Traditional Chinese Medicine (TCM) treatment

（四）临床路径标准住院日为 8-21 天。

(4) Standard length of stay: 8-21 days.

（五）进入路径标准。

(5) Criteria for CP management

1.第一诊断必须符合 ICD-10:I63 脑梗死疾病编码。

i. Primary diagnosis must be cerebral infarction (ICD10: I63);

2.当患者同时具有其他疾病诊断，但在住院期间不需要特殊处理也不影响第一诊断的临床路径流程实施时，可以进入路径。

ii. Those patients with secondary diagnosis can be covered by the current CP if they do not need special treatment for their secondary diagnosis and if the secondary diagnosis does not have any impact on the implementation of cerebral infarction pathway.

（六）住院后检查的项目。

(6) Tests

1.必需的检查项目：

i. Essential tests:

(1)血常规、尿常规;

a) Blood and urinalysis

(2)肝肾功能、电解质、血糖、凝血功能；

b) Liver and renal function, electrolytes, blood glucose, coagulation function

(3)头颅 CT、胸片、心电图。

c) Brain and skull CT, chest X-ray, ECG

2.根据具体情况可选择的检查项目：心肌酶谱、血脂、双颈动脉加双椎动脉彩超、TCD、头颅 MRI。

d) Optional tests according to patients' conditions: cardiac enzymes, lipids, dual carotid ultrasonography and double vertebral artery ultrasound, TCD, cranial MRI.

（七）选择用药。

(7) Medications

1.脱水药物：甘露醇、呋塞米等。

i. Diuretics: mannitol, furosemide .etc;

2.降压药物：收缩压大于 180mmHg 或舒张压大于 110mmHg 时，可选用卡托普利、依那普利、尼群地平、硝苯地平等

ii. Anti-hypertensives: If patients' SBP is above 180mmHg or DBP is above

110mmHg, medicines such as captopril, enalapril, nitrendipine, and nifedipine are recommended;

3.抗菌药物：按照《抗菌药物临床应用指导原则》（卫医发〔2004〕285 号）执行，无感染者不需要使用抗菌药物。明确感染患者，可根据药敏试验结果调整抗菌药物。

iii. Antibiotics referred to the Guidelines for Clinical Application of Antibacterial (Department of Medical Administration (2004) NO.285). Patients without infection do not need to use antibiotics, while patients confirmed to be infected should take antibiotics on the basis of bacterial drug sensitivity.

4.溶栓治疗：尿激酶等。

iv. Thrombolytic therapy: urokinase

5.抗凝治疗：低分子肝素、肝素等。

v. Anticoagulation therapy: Low molecular weight heparin (LMWH), heparin

6.抗血小板治疗：可选用阿司匹林、氯吡格雷等。

vi. Antiplatelet therapy: asprin and clopidogrel are recommended

7.缓泻药。

vii. Laxative

8.防治应激性溃疡：雷尼替丁、法莫替丁等。

viii. Prevent and treat stress ulcer: ranitidine, famotidine

9.纠正水、电解质紊乱药物。

ix. Medicines for fluid and electrolyte imbalance

10.中药治疗。

x. TCM treatment

（八）监测神经功能和生命体征。

(8) Monitoring neurological function and vital signs (VS).

1.生命体征监测。

i. Monitoring VS

2.监测神经系统定位体征。

ii. Monitoring focal neurological signs

（九）出院标准。

(9) Criteria for discharge

1.患者病情稳定。

i. Patient is in stable condition

2.没有需要住院治疗的并发症。

ii. There are no complications that require further inpatient care

（十）变异及原因分析。

(10) Special considerations

1.脑梗死病情危重者需转入 lCU，转入相应路径。

i. Cerebral infarction patients in a critical condition should be transferred to ICU and managed by correspondent CP;

2.辅助检查结果异常，需要复查，导致住院时间延长和住院费用增加。

ii. For abnormal diagnostic test results, reexamination is required and the cause of the abnormality needs to be analyzed, esp. those concerning prolonged length of stay and increased hospitalization costs.

3.住院期间病情加重，出现并发症，需要进一步诊治，导致住院时间延长和住院费用增加。

iii. Worsening condition, with complications that require for further diagnosis and treatment, which may lead to prolonged length of stay and increased hospitalization costs

4.既往合并有其他系统疾病，脑梗死可能导致既往疾病加重而需要治疗，导致住院时间延长和住院费用增加。

iv. Cerebral infarction may cause worsening conditions of previous comorbidities, which requires more care and may result in prolonged length of stay and increased hospitalization costs.

A2: Detailed prescribed items

脑梗死疾病临床路径表单 Cerebral infarction　Clinical pathway

疾病编码：ICD-10：I63 Code of disease：ICD-10：I63

最短住院天数：8 天最长住院天数：21 天 平均住院天数：12 天　Shortest hospital stay：8 days　Longest hospital stay：21 days Length of stay：12 days

住院日数 Hospital stay	第 1 天 day 1	医嘱名称 Prescriptions	医嘱类型 Type of prescription（PRN/SOS）	规格 Specifications	剂量 Doses	用药方法 Use	频次 Frequency	输液速度 Transfusion speed
主要诊疗工作 Diagnosis and treatment	病史采集及体格检查（包括 NIHSS 评分）Inquisition of medical history and physical examination（including NIHSS scoring）							
	评估基本生命体征 Initial assessment							

	of basic vital signs							
	完成首次病程记录及入院记录 Record keeping							
	医患沟通，交待病情 Communicating with patients about their conditions							
重点医嘱 main prescription	(一)一般项目 (1)general items	神经内科护理常规 Neurology routine nursing care	长期医嘱 PRN					
		一级护理 Grade I nursing care	长期医嘱 PRN					
		或二级护理 or Grade II nursing care	长期医嘱 PRN					
		低盐低脂饮食或流质饮食或暂禁食 Low-fat and low-salt diet or dietliquid diet or temporarily fasting	长期医嘱 PRN					

		吸氧(可选） Oxygen Inhalation(optional)	长期医嘱 PRN					
		心电监护(可选） ECG mornitoring(optional)	长期医嘱 PRN					
		监测血压(可选） Blood pressure monitoring(optional)	长期医嘱 PRN					
		保留导尿(可选） Keeping catheter (optional)	临时医嘱 SOS					
		留置导尿(可选，第一天，从入院始只做 1 次） catheter (optional in the first day and only once during hospital stay）						
		吸痰(可选）Sputum suction(optional)	临时医嘱 SOS					

	(二)检查（2）tests	血常规 Blood	临时医嘱 SOS					
		尿常规 Urine	临时医嘱 SOS					
		大便常规 Stool	临时医嘱 SOS					
		肝功能 Liver function	临时医嘱 SOS					
		肾功能 Renal function	临时医嘱 SOS					
		电解质 Electrolyte	临时医嘱 SOS					
		血糖 Blood glucose	临时医嘱 SOS					
		血脂 Blood lipid	临时医嘱 SOS					
		心肌酶谱 Myocardial enzymes	临时医嘱 SOS					
		凝血功能 Coagulation function	临时医嘱 SOS					
		同型半胱氨酸（HCY）（可选）	临时医嘱 SOS					

		(optional)						
		血气分析（可选）Blood gas analysis(optional)	临时医嘱 SOS					
		感染性疾病筛查(艾滋、梅毒、乙肝丙肝）Infectious diseases screening (AIDS, syphilis, hepatitis B or C）	临时医嘱 SOS					
		胸片 chest X-ray	临时医嘱 SOS					
		心电图 ECG	临时医嘱 SOS					
		头颅 CT （可选）Skull CT (optional)	临时医嘱 SOS				加复查不超过 3 次 less than 3 time including reexamination	

		头颅 MRI （可选） Skull MRI(optional)	临时医嘱 SOS				加复查不超过 3 次 less than 4 time including reexamination	
		头颅 CTA （可选） Skull CTA(optional)	临时医嘱 SOS				加复查不超过 3 次 less than 5 time including reexamination	
		MRA （可选） MRA(optional)	临时医嘱 SOS				加复查不超过 3 次 less than 6 time including reexamination	
		腹部彩超（可选） Abdominal ultrasonography	临时医嘱 SOS					
		经颅多普勒（TCD）（可选）	临时医嘱 SOS					
		颈动脉彩超 Carotid	临时医嘱					

		ultrasonography	SOS					
	(三)处置与手术(3) Procedures and surgeries							
		康复科医生会诊（可选） consultation with rehabilitation department(optional)	临时医嘱 SOS				住院 1-3 天内执行一次 execute within 1-3 days	
	(四)药剂(4)drugs	溶栓治疗:（有适应症时,仅第一天用一次）Thrombolytic therapy(patients with indications, only once in the first day during the stay)						
		1.尿激酶 urokinase		10 万 IU 100 thousand IU	100-150 万 IU 1-1.5 million IU			

		0.9%生理盐水 0.9% normal saline(NS)	临时医嘱 SOS	100ml	100ml	静脉滴注 intravenous drip	qd	半小时内滴完 within half an hour
		抗血小板药物：（二选一或同时用）Antiplatelet agents：(use alternative or both)						
		1.阿司匹林肠溶片 Aspirin enteric-coated tablets	长期医嘱 PRN	100mg	100-300mg	口服 oral	qn(睡前）(before sleep)	
		2.氯吡格雷片 Clopidogrel hydrogen sulfate Tablets	长期医嘱 PRN	75mg	75mg	口服 oral	qd	
		抗动脉粥样硬化药物：Anti atherosclerotic drugs：						
		1.辛伐他汀咀嚼片 Simvastatin	长期医嘱 PRN	20mg	20mg	口服 oral	qd	

		Chewable Tablets						
		抗自由基药物： （可选）Free redical scavenger(optional)						
		1.依达拉奉 Edaravone	长期医嘱 PRN	30mg	30mg	静脉滴注 intravenous drip	bid	35-45 滴/分 drops/min
		0.9%生理盐水 0.9% NS		100ml	100ml	静脉滴注 intravenous drip	bid	35-46 滴/分 drops/min
		改善脑灌注药物： （可选，3 选 1） Drugs for improving cerebral perfusion (optional, use 1 type out follow 3 one)						
		1.注射用倍他司丁 Betahistine for injection	长期医嘱 PRN	20mg	20mg	静脉滴注 intravenous drip	qd	

		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		2.丹红注射液 danhong injection	长期医嘱 PRN	20-30ml	20-30ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		3.疏血通注射液 Shuxuetong injection	长期医嘱 PRN	2ml	6ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		支持治疗（可选） Supportive treatment(optional)						
		1.5%葡萄糖液 5% Glucose liquid	临时医嘱 SOS	250ml/500ml	250ml-500ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min

		门冬氨酸钾镁注射液 potassium-magnesium aspartate injection		2g	2g	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		肌苷针 Inosine injection		400mg	400mg	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		氯化钾注射液 Potassium chloride injection		5ml/10ml	5ml/10ml		qd	35-45 滴/分 drops/min
		2.复方氨基酸液 Compound amino acid	临时医嘱 SOS	250ml	250ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		扩容药物： dilatation durg						
		1.羟乙基淀粉 hydroxyethyl starch	长期医嘱 PRN	500ml	500ml	静脉滴注 intravenous drip	qd	
	(五)其他							

主要护理工作 Main nursing care	入院卫生教育 Health education on admission							
	入院护理评估 Nursing assessment on admission							
	患者检查指导 Instruct patients on tests							
	住院基础护理 Basic nursing care on admission							
	脑血管病的健康宣教，戒烟宣教 Advise on smoking cessation and health education on cerebrovascular disease							
	饮食指导 Instruction on diets							
	观察患者病情变化 Observing conditions of patient							

	测血压、体温、脉搏 Measuring blood pressure,temperature and pulse							
住院日数 Hospital stay	第 2 天 day 2	医嘱名称 Prescriptions	医嘱类型 Type of prescription（PRN/SOS）	规格 Specifications	剂量 Doses	用药方法 Use	频次 Frequency	输液速度 Transfusion speed
主要诊疗工作 Dianosis and treatment	主治医师查房，书写上级医师查房记录 Ward round by chief physician and keep record senior doctors							
	评价神经功能状态 Evaluation of nerval function							
	评估辅助检查结果 Assessment of auxiliary examination							

	outcomes							
	必要时多科会诊 Joint consultation with physicians when necessary							
	开始康复治疗							
	需手术者转神经外科 Transfer to neurosurgery department when patients need surgeries							
	记录会诊意见 Keeping record of consultation							
重点医嘱 main prescription	(一)一般项目(1) General items							
		神经内科护理常规 Neurology routine nursing care	长期医嘱 PRN					
		一级护理 Grade I nursing care	长期医嘱 PRN					

		或二级护理 or Grade II nursing care	长期医嘱 PRN					
		低盐低脂饮食或流质饮食或暂禁食 Low-fat and low-salt diet or dietliquid diet or temporarily fasting	长期医嘱 PRN					
		吸氧(可选） Oxygen Inhalation(optional)	长期医嘱 PRN					
		心电监护(可选） ECG mornitoring(optional)	长期医嘱 PRN					
		监测血压(可选） Blood pressure monitoring(optional)	长期医嘱 PRN					
		保留导尿(可选） Keeping catheter (optional)	临时医嘱 SOS					
		吸痰(可选）Sputum suction(optional)	临时医嘱 SOS					

	(二)检查(3) Procedures and surgeries	复查异常化验 retest abnormal laboratory test	临时医嘱 SOS					
		复查头 CT 或 MRI （必要时） reexamine skull CT or MRI(if necessary)	临时医嘱 SOS				加复查不超过 3 次 less than 6 time including reexaminatio n	
	(三)处置与手术(3) Procedures and surgeries							
		康复科医生会诊 （可选） consultation with rehabilitation department(optional)	临时医嘱 SOS				住院 1-3 天内执行一次 execute within 1-3 days	
	(四)药剂(4)drugs							
		抗血小板药物： （二选一或同时用）Antiplatelet agents：(use alternative or both)						

		1.阿司匹林肠溶片 Aspirin enteric-coated tablets	长期医嘱 PRN	100mg	100-300mg	口服 oral	qn(睡前） (before sleep)	
		2.氯吡格雷片 Clopidogrel hydrogen sulfate Tablets	长期医嘱 PRN	75mg	75mg	口服 oral	qd	
		抗动脉粥样硬化药物： Antiatherosclerotic drugs：						
		1.辛伐他汀咀嚼片 Simvastatin Chewable Tablets	长期医嘱 PRN	20mg	20mg	口服 oral	qd	
		抗自由基药物： （可选）Free redical scavenger(optional)						
		1.依达拉奉 Edaravone	长期医嘱 PRN	30mg	30mg	静脉滴注 intravenous drip	bid	35-45 滴/分 drops/min

		0.9%生理盐水 0.9% NS		100ml	100ml	静脉滴注 intravenous drip	bid	35-46 滴/分 drops/min
		改善脑灌注药物：（可选，3 选 1）Drugs for improving cerebral perfusion (optional, use 1 type out follow 3 one)						
		1.注射用倍他司丁 Betahistine for injection	长期医嘱 PRN	20mg	20mg	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		2.丹红注射液 danhong injection	长期医嘱 PRN	20-30ml	20-30ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			

		3.疏血通注射液 Shuxuetong injection	长期医嘱 PRN	2ml	6ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		支持治疗（可选） Supportive treatment(optional)						
		1.5%葡萄糖液 5% Glucose liquid	临时医嘱 SOS	250ml/500ml	250ml-500ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		门冬氨酸钾镁注射液 potassium-magnesium aspartate injection		2g	2g	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		肌苷针 Inosine injection		400mg	400mg	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		氯化钾注射液 Potassium chloride injection		5ml/10ml	5ml/10ml		qd	35-45 滴/分 drops/min

		2.复方氨基酸液 Compound amino acid	临时医嘱 SOS	250ml	250ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		扩容药物：dilatation durg						
		1.羟乙基淀粉 hydroxyethyl starch	长期医嘱 PRN	500ml	500ml	静脉滴注 intravenous drip	qd	
	(五)其他(5) Others							
主要护理工作 Main nursing care	护理评估 Nursing assessment							
	基础护理 Basic nursing care							
	脑血管病的健康宣教，戒烟宣教 Advise on smoking cessation and health education on cerebrovascular disease							
	饮食指导							

	Instruction on diets							
	观察患者病情变化 Observing conditions of patient							
住院日数 Hospital stay	第 3-7 天 day 3-7	医嘱名称 Prescriptions	医嘱类型 Type of prescription（PRN/SOS）	规格 Specifications	剂量 Doses	用药方法 Use	频次 Frequency	输液速度 Transfusion speed
主要诊疗工作 Dianosis and treatment	各级医生查房，书写查房记录 Ward round by chief physician and keep record senior doctors							
	评价神经功能状态 Evaluation of nerval function							
	评估辅助检查结果 Assessment of auxiliary examination							

	outcomes							
	继续防治并发症 prevent and treat complication							
	必要时多科会诊 Joint consultation with physicians when necessary							
	开始康复治疗							
	需手术者转神经外科 Transfer to neurosurgery department when patients need surgeries							
重点医嘱 main prescription	(一)一般项目(1) General items	神经内科护理常规 Neurology routine nursing care	长期医嘱 PRN					
		一级护理 Grade I nursing care	长期医嘱 PRN					
		或二级护理 or Grade II nursing care	长期医嘱 PRN					

		低盐低脂饮食或流质饮食或暂禁食 Low-fat and low-salt diet or dietliquid diet or temporarily fasting	长期医嘱 PRN					
		吸氧(可选） Oxygen Inhalation(optional)	长期医嘱 PRN					
		心电监护(可选） ECG mornitoring(optional)	长期医嘱 PRN					
		监测血压(可选） Blood pressure monitoring(optional)	长期医嘱 PRN					
		保留导尿(可选） Keeping catheter (optional)	临时医嘱 SOS					
		吸痰(可选）Sputum suction(optional)	临时医嘱 SOS					
			临时医嘱 SOS					

	(二)检查(2)tests	复查异常化验 retest abnormal laboratory test	临时医嘱 SOS					
	(三)处置与手术(3) Procedures and surgeries							
		康复科医生会诊（可选） consultation with rehabilitation department(optional)	临时医嘱 SOS				住院 1-3 天内执行一次 execute within 1-3 days	
	(四)药剂(4)drugs							
		抗血小板药物：（二选一或同时用）Antiplatelet agents：(use alternative or both)						
		1.阿司匹林肠溶片 Aspirin enteric-coated tablets	长期医嘱 PRN	100mg	100-300mg	口服 oral	qn(睡前） (before sleep)	
		2.氯吡格雷片 Clopidogrel hydrogen sulfate	长期医嘱 PRN	75mg	75mg	口服 oral	qd	

		Tablets						
		抗动脉粥样硬化药物：Antiatherosclerotic drugs：						
		1.辛伐他汀咀嚼片 Simvastatin Chewable Tablets	长期医嘱 PRN	20mg	20mg	口服 oral	qd	
		抗自由基药物：（可选）Free redical scavenger(optional)						
		1.依达拉奉 Edaravone	长期医嘱 PRN	30mg	30mg	静脉滴注 intravenous drip	bid	35-45 滴/分 drops/min
		0.9%生理盐水 0.9% NS		100ml	100ml	静脉滴注 intravenous drip	bid	35-46 滴/分 drops/min

		改善脑灌注药物： （可选，3 选 1） Drugs for improving cerebral perfusion (optional, use 1 type out follow 3 one)						
		1.注射用倍他司丁 Betahistine for injection	长期医嘱 PRN	20mg	20mg	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		2.丹红注射液 danhong injection	长期医嘱 PRN	20-30ml	20-30ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		3.疏血通注射液 Shuxuetong injection	长期医嘱 PRN	2ml	6ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5%		250ml	250ml			

		Glucose liquid						
		支持治疗（可选） Supportive treatment(optional)						
		1.5%葡萄糖液 5% Glucose liquid	临时医嘱 SOS	250ml/500ml	250ml-500ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		门冬氨酸钾镁注射液 potassium-magnesium aspartate injection		2g	2g	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		肌苷针 Inosine injection		400mg	400mg	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		氯化钾注射液 Potassium chloride injection		5ml/10ml	5ml/10ml		qd	35-45 滴/分 drops/min
		2.复方氨基酸液 Compound amino acid	临时医嘱 SOS	250ml	250ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		扩容药物：						

		dilatation durg						
		1.羟乙基淀粉 hydroxyethyl starch	长期医嘱 PRN	500ml	500ml	静脉滴注 intravenous drip	qd	
	(五)其他(5) Others							
主要护理工作 Dianosis and treatment	护理评估 Nursing assessment							
	基础护理 Basic nursing care							
	脑血管病的健康宣教，戒烟宣教 Advise on smoking cessation and health education on cerebrovascular disease							
	饮食指导 Instruction on diets							
	观察患者病情变化 Observing conditions of patient							

住院日数 Hospital stay	第 8-21 天 day 8-21	医嘱名称 Prescriptions	医嘱类型 Type of prescription（PRN/SOS）	规格 Specifications	剂量 Doses	用药方法 Use	频次 Frequency	输液速度 Transfusion speed
主要诊疗工作 Dianosis and treatment	各级医生查房 Ward round by physicians							
	评估辅助检查结果 Assessment of auxiliary examination outcomes							
	评价神经功能状态 Evaluation of nerval function							
	继续防治并发症 Keeping preventing and treating complications							
	必要时相关科室会诊 Joint consultation with related physicians							

	when necessary							
	康复治疗							
	通知患者及其家属出院 Inform patients and his/her relatives of the discharge day							
	向患者交待出院后注意事项，预约复诊日期 Educate patients on do's and don’ts upon discharge and make appointment for date of reexamination							
	如果患者不能出院，在“病程记录”中说明原因和继续治疗的方案 Record follow-on							

	treatment and reasons if patients can not be discharged							
重点医嘱 main prescription	(一)一般项目	神经内科护理常规 Neurology routine nursing care	长期医嘱 PRN					
		一级护理 Grade I nursing care	长期医嘱 PRN					
		或二级护理 or Grade II nursing care	长期医嘱 PRN					
		低盐低脂饮食或流质饮食或暂禁食 Low-fat and low-salt diet or dietliquid diet or temporarily fasting	长期医嘱 PRN					
		吸氧(可选） Oxygen Inhalation(optional)	长期医嘱 PRN					
		心电监护(可选） ECG mornitoring(optional	长期医嘱 PRN					

		)						
		监测血压(可选） Blood pressure monitoring(optional)	长期医嘱 PRN					
	(二)检查	头颅 MRI （可选） Skull MRI(optional)	临时医嘱 SOS				加复查不超过 3 次 less than 6 time including reexamination	
		头颅 CTA（可选） Skull CTA(optional)	临时医嘱 SOS				加复查不超过 3 次 less than 6 time including reexamination	
		头颅 MRA（可选）Skull MRA(optional)	临时医嘱 SOS				加复查不超过 3 次 less than 6 time including reexamination	

	(三)处置与手术							
	(四)药剂							
		抗血小板药物：（二选一或同时用）Antiplatelet agents：(use alternative or both)						
		1.阿司匹林肠溶片 Aspirin enteric-coated tablets	长期医嘱 PRN	100mg	100-300mg	口服 oral	qn(睡前）(before sleep)	
		2.氯吡格雷片 Clopidogrel hydrogen sulfate Tablets	长期医嘱 PRN	75mg	75mg	口服 oral	qd	
		抗动脉粥样硬化药物：Antiatherosclerotic drugs：						
		1.辛伐他汀咀嚼片 Simvastatin Chewable Tablets	长期医嘱 PRN	20mg	20mg	口服 oral	qd	

		抗自由基药物： （可选）Free redical scavenger(optional)						
		1.依达拉奉 Edaravone	长期医嘱 PRN	30mg	30mg	静脉滴注 intravenous drip	bid	35-45 滴/分 drops/min
		0.9%生理盐水 0.9% NS		100ml	100ml	静脉滴注 intravenous drip	bid	35-46 滴/分 drops/min
		改善脑灌注药物： （可选，3 选 1） Drugs for improving cerebral perfusion (optional, use 1 type out follow 3 one)						
		1.注射用倍他司丁 Betahistine for injection	长期医嘱 PRN	20mg	20mg	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			

		2.丹红注射液 danhong injection	长期医嘱 PRN	20-30ml	20-30ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		3.疏血通注射液 Shuxuetong injection	长期医嘱 PRN	2ml	6ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		支持治疗（可选） Supportive treatment(optional)						
		1.5%葡萄糖液 5% Glucose liquid	临时医嘱 SOS	250ml/500ml	250ml-500ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		门冬氨酸钾镁注射液 potassium-magnesium aspartate injection		2g	2g	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min

		肌苷针 Inosine injection		400mg	400mg	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		氯化钾注射液 Potassium chloride injection		5ml/10ml	5ml/10ml		qd	35-45 滴/分 drops/min
		2.复方氨基酸液 Compound amino acid	临时医嘱 SOS	250ml	250ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		扩容药物： dilatation durg						
		1.羟乙基淀粉 hydroxyethyl starch	长期医嘱 PRN	500ml	500ml	静脉滴注 intravenous drip	qd	
	(五)其他(5) Others							
主要护理工作 Dianosis and treatment	正确执行医嘱 Correctly perform prescriptions							
	观察患者病情变化 Observing conditions of							

	patient							
住院日数 Hospital stay	出院日 Day of discharge	医嘱名称 Prescriptions	医嘱类型 Type of prescription（PRN/SOS）	规格 Specifications	剂量 Doses	用药方法 Use	频次 Frequency	输液速度 Transfusion speed
主要诊疗工作 Dianosis and treatment	再次向患者及家属介绍病出院后注意事项，出院后治疗及家庭保健 Educate patients on do's and don’ts, treatments and family health care after discharge							
	患者办理出院手续，出院 Patients check out，discharge							

重点医嘱 main prescription	(一)一般项目(1) General items	神经内科护理常规 Neurology routine nursing care	长期医嘱 PRN					
		二级护理 Grade II nursing care	长期医嘱 PRN					
		或三级护理 or Grade III nursing care	长期医嘱 PRN					
		低盐低脂饮食或流质饮食 Low-fat and low-salt diet or dietliquid diet	长期医嘱 PRN					
		今日出院 Discharge						
	(二)检查(2) Tests	复查异常化验 Take tests when reexamination is abnormal	临时医嘱 SOS					
		复查头颅 CT 或 MRIReexamine skull CT or MRI	临时医嘱 SOS				加复查不超过 3 次 less than 6 time including reexamination	

	(三)处置与手术(3) Procedures and surgeries							
	(四)药剂(4) Drugs							
		抗血小板药物：（二选一或同时用）Antiplatelet agents：(use alternative or both)						
		1.阿司匹林肠溶片 Aspirin enteric-coated tablets	长期医嘱 PRN	100mg	100-300mg	口服 oral	qn(睡前）(before sleep)	
		2.氯吡格雷片 Clopidogrel hydrogen sulfate Tablets	长期医嘱 PRN	75mg	75mg	口服 oral	qd	
		抗动脉粥样硬化药物：Antiatherosclerotic drugs：						
		1.辛伐他汀咀嚼片 Simvastatin	长期医嘱 PRN	20mg	20mg	口服 oral	qd	

		Chewable Tablets						
		抗自由基药物： （可选）Free redical scavenger(optional)						
		1.依达拉奉 Edaravone	长期医嘱 PRN	30mg	30mg	静脉滴注 intravenous drip	bid	35-45 滴/分 drops/min
		0.9%生理盐水 0.9% NS		100ml	100ml	静脉滴注 intravenous drip	bid	35-46 滴/分 drops/min
		改善脑灌注药物： （可选，3 选 1） Drugs for improving cerebral perfusion (optional, use 1 type out follow 3 one)						
		1.注射用倍他司丁 Betahistine for injection	长期医嘱 PRN	20mg	20mg	静脉滴注 intravenous drip	qd	

		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		2.丹红注射液 danhong injection	长期医嘱 PRN	20-30ml	20-30ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		3.疏血通注射液 Shuxuetong injection	长期医嘱 PRN	2ml	6ml	静脉滴注 intravenous drip	qd	
		生理盐水 0.9% NS		250mg	250mg			
		或 5%葡萄糖 5% Glucose liquid		250ml	250ml			
		支持治疗（可选） Supportive treatment(optional)						
		1.5%葡萄糖液 5% Glucose liquid	临时医嘱 SOS	250ml/500ml	250ml-500ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min

		门冬氨酸钾镁注射液 potassium-magnesium aspartate injection		2g	2g	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		肌苷针 Inosine injection		400mg	400mg	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		氯化钾注射液 Potassium chloride injection		5ml/10ml	5ml/10ml		qd	35-45 滴/分 drops/min
		2.复方氨基酸液 Compound amino acid	临时医嘱 SOS	250ml	250ml	静脉滴注 intravenous drip	qd	35-45 滴/分 drops/min
		扩容药物： dilatation durg						
		1.羟乙基淀粉 hydroxyethyl starch	长期医嘱 PRN	500ml	500ml	静脉滴注 intravenous drip	qd	
	(五)其他(5) Others							
主要护理	出院带药服用指导 Instruction on take-							

工作 Dianosis and treatment	away drugs							
	特殊护理指导 Instruction on special nursing care							
	告知复诊时间和地点 Tell patients time and place of reexamination							
	交待常见的药物不良反应 Inform patients about common adverse drug reaction							
	嘱其定期门诊复诊 Inform patients about regular follow-up visit							

Appendix B

B1: Search strategy

a. Medline—Ovid—1288 papers

Concepts	Clinical Pathways	Acute Cerebral Infarction	RCT
Author Keywords:	clinical path*.mp. critical path*.mp. care map*.mp. care plan*.mp. care path*.mp. clinical record*.mp. anticipatory recovery pathway*.mp. ((multidisciplinary OR interdisciplinary OR Integrated) AND care*).mp. managed care.mp. (integrated AND system*).mp. (clinical AND protocol*).mp.	Cerebral Infarction *.mp. apoplexy*.mp. cerebrovascular*.mp. brain Vascular Accident*.mp. brain infarction*.mp. brain ischemias*.mp. lacunar*.mp. cerebral*.mp. (Intracranial AND Vascular).mp. Basal Ganglia Vascular*.mp.	(Controlled AND randomized AND trial*).mp. (double-blind or double-masked).mp. (single-blind or single-masked).mp.
Subject Headings: MeSH EMTREE CINAHL terms	patient care planning/ critical pathways/ case management/ managed care programs/ delivery of Health Care, Integrated/ patient care management/ exp patient care team/ clinical Protocols/	exp cerebrovascular disorders/	exp randomized controlled trials as topic/ randomized controlled trial.pt. controlled clinical trials as topic/ Random allocation/ double-blind method/ single-blind method/

b. Medline—Pubmed—15 papers

Concepts	Clinical Pathways	Acute Cerebral Infarction	RCT
Author Keywords:	clinical pathway*.tw. care pathway*.tw. critical path*.tw. care map*.tw. care plan*.tw. care path method.tw. clinical record*.tw. anticipatory recovery pathway*.tw. (multidisciplinary AND care*).tw. (care AND pathway*).tw.	Cerebral Infarction *.tw. apoplexy*.tw. cerebrovascular*.tw. brain Vascular Accident*.tw. brain infarction*.tw. brain ischemias*.tw. lacunar*.tw. cerebral*.tw.	randomized trial*.tw. randomized controlled trial*.tw. random*.tw. clinical trial*.tw.
Subject Headings: MeSH EMTREE	critical pathway [Mesh] patient care planning [Mesh] (inclusive of case management and critical	Cerebral Infarction [Mesh] brain	randomized controlled trials as topic*[Mesh] randomized controlled trial.pt.

CINAHL terms	pathways)	infarction*[Mesh] brain ischemias*[Mesh]	controlled clinical trials as topic[Mesh] clinical trials*[Mesh] Intention to Treat Analysis[Mesh] random allocation[Mesh]

c. Cochrane Library—236 papers

Concepts	**Clinical Pathways**	**Acute Cerebral Infarction**	**RCT**
Author Keywords:	(Clinical pathway* or Care pathway* or Critical pathway* or Care path method or Care map$ or care plan$) :ti,ab,kw	Cerebral Infarction *:ti,ab,kw (apoplexy*or apoplexia*):ti,ab,kw cerebrovascular*:ti,ab,kw brain Vascular Accident*:ti,ab,kw (brain AND infarction*):ti,ab,kw (brain AND ischemias*):ti,ab,kw (brain attack* or brain accident*):ti,ab,kw (brain AND hemorrhage*):ti,ab,kw	randomized trial*:ti,ab,kw. randomized controlled*:ti,ab,kw
Subject Headings: MeSH EMTREE CINAHL terms	MeSH descriptor: [Critical Pathways]	MeSH descriptor: [Cerebral Infarction] explode all trees MeSH descriptor: [Brain Ischemia] explode all trees MeSH descriptor: [Cerebral Hemorrhage] explode all trees MeSH descriptor: [Cerebral Infarction] explode all trees	MeSH descriptor: [Randomized Controlled Trial] explode all trees MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees

d. EMBASE—OVID—339 papers

Concepts	**Clinical Pathways**	**Acute Cerebral Infarction**	**RCT**
Author Keywords:	clinical path*.mp. critical path*.mp. care map*.mp. care plan*.mp. care path*.mp. clinical record*.mp. anticipatory recovery pathway*.mp. ((multidisciplinary OR interdisciplinary OR Integrated) AND care*).mp. managed care.mp. (integrated AND system*).mp.	Cerebral Infarction *.mp. (apoplexy*or apoplexia*).mp. cerebrovascular*.mp. brain Vascular Accident*.mp. (brain AND infarction*).mp. (brain AND ischemias*).mp. (brain attack* or brain accident*).mp. (brain AND hemorrhage*).mp.	randomized Controlled*.mp. (double blind or double masked).mp. (single blind or single masked).mp.
Subject Headings: MeSH EMTREE CINAHL	nursing care plan/ clinical pathway/	exp cerebrovascular accident/ exp brain hemorrhage/ exp brain infarction/ exp brain ischemia/	randomized controlled trial/ randomized controlled trial (topic)/ double blind procedure/

terms			single blind procedure/

CINAHL—6 papers

Concepts	Clinical Pathways	Acute Cerebral Infarction	RCT
Author Keywords:	(Clinical pathway* or Care pathway* or Critical pathway* or Care path method or Care map$ or care plan$).	Cerebral Infarction *:ti,ab,kw (apoplexy*or apoplexia*):ti,ab,kw cerebrovascular*:ti,ab,kw brain Vascular Accident*:ti,ab,kw (brain AND infarction*):ti,ab,kw (brain AND ischemias*):ti,ab,kw (brain attack* or brain accident*):ti,ab,kw (brain AND hemorrhage*):ti,ab,kw	(randomized Controlled*).mp.
Subject Headings: MeSH EMTREE CINAHL terms	critical path	Stroke stroke patients	Randomized controlled trials

PubMed: Cost-effectiveness search strategy

Search	Query	Results
1	"Stroke"[Mesh]	122097
2	("Critical Pathways"[Mesh]) AND ("Cost-Benefit Analysis"[Mesh])	217
3	(#1) AND (#2)	6

B2: Summary of study characteristics

Author, Country& Year	Method	Duration	Sample size	Intervention	Controls	Outcomes	Conclusion/Discussion
Dominique A et al,2004,(Australia)	RCT parallel group	13months	468	Stroke Unit (SU) multidisciplinary team	mobile services (MS),and conventional care (CC)	Overall processes of care (PoC) **adherence rates** was 75% in SU,65% in MS,52% in CC. The adjusted odds of participants **being alive** at discharge (aOR 3.63; 95% CI: 1.04 to 12.66;p=0.043). 28 weeks after stroke, **trends** at home (aOR 3.09; 95% CI: 0.96 to 9.87;p=0.058) and **independent** (aOR 2.61; 95% CI: 0.96 to 7.10;p=0.061).	1)Better adherence to key PoC in SUs 2)better adherence was associated with improved mortality at discharge and insignificant trends found with independence at home after discharge.

Middleton S. et al,2011,(Australia)	cluster RCT	45 months	1696	proactive multidisciplinary evidence-based practical protocols (supported by training) for the management of fever, hyperglycemia, and swallowing dysfunction	abridged version of existing guidelines	**Death &dependency**[95%CI(5.8 to 25.4), P=0.002], **functional dependency** (Barthel index≥95:95%CI(-0.5 to 19.5),p=0.07 Barthel index≥60:95%CI(-3.6to 8.6),p=0.44), and **SF-36** (PCS score:95%CI(1.2 to 5.5), P=0.002; MSCscore:95%CI(-1.9 to 2.8), P=0.69). **Fever**: 95%CI(8.3% to 24.6%), P<0.0001, **Glucose:** 95%CI(0.08 to 1.01), P=0.02, **Swallowing screening**:95%CI(22% to 36.4%), P<0.0001, **Length ofhospital stay**: 95%CI(-0.5 to 3.5), P<0.144.	Adoption of protocals favor patient outcomes after 90-day discharge.

Assunta De Luca et al,2009,(Italy)	cluster RCT	6 months	2547	Emergency Clinical Pathways (ECP) applied in Emergency Medical Service (EMS) and Emergency Room (ER),with adoption of specific protocols and standardized procedures, supported by educational training in line with the experiential learning tradition	conventional EMS and ER treatment	**1) Eligible patients referred to SU:** ITT analysis: aRR=2.01, 95% CI(0.79, 4.00);PP analysis: aRR 3.21, 95% CI (1.62, 4.98). 2) **Eligible stroke patients receiving thrombolysis in SU tested by Fisher's exact tests:** ITT analysis P=0.02, PP analysis: P=0.001. 3) **The EMS treatment/travel mean time (SD) from dispatch to hospital (minutes) in metropolitan area:** Intervention group :31.8 (15.1); control group: 35.8 (13.8). 4) **The ER transferred mean time (SD) in metropolitan area: Intervention group**: 193 (176); control group 228 (216).	ECP is potential efficient and feasible
DengYM et al,2014,(China)	RCT parallel group	8 months	TIA:426;ICH:332	Fine tune recommended protocols for TIA and ICH based on national CP	converntional healthcare	1) TIA: **length of hospital stay**(p<0.01), **hospitalization cost** (p=0.02), **drug cost** (p=0.04), **Incidence** of stroke within 90 days (p=0.16) 2) ICH: **length of hospital stay**(p<0.01), **hospitalization cost** (p<0.01), **drug cost** (p<0.01), **mortality**(p=0.72), **infection** (p=0.07)3) The **NIHSS** between groups at admission (p=0.48); 14 days after admission (p=0.10). 4) The **Barthel Index** between groups at admission (p=0.60); after 90 days (p=0.12).	1) Both TIA and ICH clinical pathways decreased the length of hospital stay and overall healthcare costs. 2) no sacrifice of treatment quality was observed.

Drury P et al,2013,(Australia)	A cluste RCT	45 months	1804	Proactive multidisciplinary evidence-based practical protocols (supported by training) for the management of fever, hyperglycemia, and swallowing dysfunction	abridged version of existing guidelines	1)more patients admitted to hospitals allocated to the intervention group received care according to the **fever** (95%CI(7.9 to 22%), P < 0.001), **hyperglycemia** (95%CI(0.8 to 6.3%),P = 0.01), and **swallowing dysfunctio**n protocols (95%CI(5.5 to 21%), P ≤ 0.001).2)Significantly more patients in intervention stroke units received **four-hourly temperature monitoring** (37% vs. 19%, P < 0.001) and **six-hourly glucose monitoring** (32% vs. 9.5%, P < 0.001) within 72 hours of admission to a stroke unit, and a **swallowing screen** (46% vs.6.8%, P ≤ 0.0001) within the first 24 hours of admission to hospital.3) No difference between the groups in the treatment of patients with fever with paracetamol (21% vs.29%, P = 0.78) or their hyperglycemia with insulin (40% vs.30%, P = 0.49).	1)significantly more patients were managed, demonstrating a clear positive influence of intervention on behavior change. 2)There was no difference between the groups in the treatment of fever and hyperglycemia, which was unable to explain definitively the large improvements in death and dependency found in the main trial results.

Fagerberg B et al,2000,(Sweden)	2:1 RCT	15 months	249	acute stroke unit care integrated with geriatric wards in term of treatment principles, training and work procedures	conventional treatment in acute stroke unit	1) No significant difference in **mortality rates** after 1 year by discharge [80% vs 72%, 95 CI (-4%-18%)]. 2) No significant difference in **proportion of patients at home** after 3 weeks [46% vs 44%, 95 CI (-11%-16%)], 3 months [68% vs 61%, 95 CI (-7%-19%)]and 12 months [61% vs 59%, 95 CI (-11%-15%)].3) No significant differences between the groups in the **neurological score** or in the **ADL scores**, and in mean **total Nottingham Health Profile scores**. 4) In patients with concomitant cardiac disease, there was a **reduction in death or institutional care after 3 months** (28% versus 49%, 95% CI -40% to -3%). 4)The mean **length of stay** after the index hospitalization was 28.3 (median 15) days in the acute stoke units integrated with a care continuum and 35.8 (median 10) days in the general ward group (P=NS).	Limited short-term benificial effect was found, no significant difference on the healthoutcome after 1 year.

Panella M et al,2012,(Italy)	A cluster RCT	2 years	476	a trained multidisciplinary team developed practical CPs and reviewd by regional EBM (evidence-based medicine) unit	usual care	1) lower risk of **mortality at 7 days**(OR = 0.10; 95% CI[0.01 to 0.95],p=0.04).No significant differences in **mortality at 30 days**(OR = 0.30; 95% CI [0.06 to 1.39], p=0.12) .2) Lower rate of not returning to pre-stroke function (OR = 0.42; 95% CI [0.18 to 0.98],p=0.04). 3) less but non-significant **length of stay**mean(SD): intervention (11.78±6.6) v.s.control (10.88±7.9, p=0.19). 4) Plenty of process of care performed better in CP arm.	CPs can significantly improve the outcomes of patients with ischemic patients with stroke

Sulch D et al,2000,(UK)	RCT parallel group	N/A	152	Integrated Care Pathway (multidisciplinary team organized, evidence-based, goal-defined, and time-managed plan),covered all aspects of inpatient rehabilitation from admission (assessments) to discharge	conventional multidisciplinary team care (MTD)	1) No differences in **mortality** rates (13% vs 8%, OR=0.6, 95%CI[0.3;2.3]), **institutionalization** (13% vs 21%, OR=01.5, 95%CI[0.5;2.8]), or **length of hospital stay** (50±19 vs 45±23 days) between two groups. 2) **median change in BI score between 4 and 12 weeks** improved sigificantlt in control group 6 versus 2; P<0.01. 3) **control group had higher Quality of Life scores at 26 weeks**: 72 versus 63; P<0.005.4) There were no significant differences in the **mean duration of physiotherapy** (42.8±41.2 versus 39.4±36.4 hours) or **occupational therapy** (8.5±7.5 versus 8.0±7.5 hours) received between the 2 groups.	ICP management offered no benefit over MTD on a stroke rehabilitation unit.

Torp CR et al,2006,(Denmark)	RCT parallel group	2 years	198	interdisciplinary stroke team focusing on personal continuous discharge planning in order to reduce functional loss after discharge	standard aftercare	1) No significant difference in terms of **length of hospital admission** (35.2 versus 39.8 days, 95%CI[-12.4 days; 3.1 days]). 2) No signficantdifferneces in **readmission,GP-visit**s, and **primary health care services** and in **functional scores** or **patient satisfaction**. 3) No significant differences were found as regards**BI, Mini mental state examination, SF-36.**	Interdisciplinary stroke team offered no benefit over standard aftercare

B3: Detailed statement for the assessment of risk of bias

Study	Sequence generation	Allocation concealment	Blinding of participants & Personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Dominique A et al,2004,Australia	High risk of Bias: Cohort design, allocation by availability of the intervention	Uncertainty: the method of concealment is not described.	Low risk of Bias: researchers collecting follow-up data were blinded to the model of care.	Low risk of Bias:1) Although only 15 of the 21 PoCs were used in the analysis, the selection criteria included consideration of reliability, robustness and importance regarding outcome.2) The outcome data were available on 96% of selected patients.	High risk of bias: no detailed reporting on the selected PoCs	High risk of bias: 1)potential for contamination and crossovers among groups;2) The thorough and complete care rates may have been overestimated.
Middleton S. et al,2011,Australia	Low risk of Bias:1) random number generating software; 2)ASUs were stratified by category;	Low risk of Bias: Stratifcation with allocation concealed until provided to the project officer who assigned ASUs to groups.	Low risk of bias:1)Research assistants were masked to trial design enrolled patients, trial aims, design and group allocation. The statistician was masked to group allocation. 2) Single blind: clinician delivering the intervention were not blinded.	Low risk of bias: 1)The patients with severe strokes might be underestimated, but the subgroup analyses has showed significant outcomes accordingly. 2) 48 out of 735 patients were lost to follow-up.	Low risk of bias: all primary and secondary outcomes were reported completely.	Low risk of bias:the study appears to be free of other sources of bias.
Assunta De Luca et al,2009,Italy	Low risk of Bias: Utilized the Italian lottery number extracted on the 6th of November 2004 as seed numbers for generating the random sequences.	High risk of bias: just health professionals in the control group were not aware of being part of the study.	High risk of bias:the EMS intervention arm had a lower rate of confirmed strokes than the control arm, suggesting possible over-diagnosing by the trained EMS personnel	High risk of Bias:1) Direct access to CT which, according to the protocol, together with time of onset was necessary to define the eligible stroke patients, was not available in the whole study population. 2)The province of Viterbo did not complete the study, meaning that 10 entities with 1086 patients withdrew, 985 from the intervention and 100 from the control arm.	Low risk of Bias: all proposed outcomes were reported clearly.	High risk of Bias:Strong non homogeneity among clusters and withdrawal of some important participantingcentres reduced the power of the study. Low rsk of Bias:"stopping rules": the study strictly monitored the study in aim to detect any unexpected events.

DengYM et al,2014, China	Uncertainty: insufficient information about the sequence generation process to permit judgement.	Uncertainty: insufficient information about the sequence generation process to permit judgement.	Uncertainty: insufficient information about the sequence generation process to permit judgement.	Low risk of bias: no mssing outcome data	Low risk of bias: all primary and secondary outcomes were reported completely.	Uncertainty:insufficient information to assess whether an important risk of bias exists.
Drury P et al,2013,Australia	Low risk of Bias:1) random number generating software; 2)ASUs were stratified by category;	Low risk of Bias: Stratifcation with allocation concealed until provided to the project officer who assigned ASUs to groups.	Low risk of bias:1)Research assistants were masked to trial design enrolled patients, trial aims, design and group allocation. The statistician was masked to group allocation. 2) Single blind: clinician delivering the intervention were not blinded. 3) 4 auditors blind to study design conducted audit.	Low risk of bias: 1)The patients with severe strokes might be underestimated, but the subgroup analyses has showed significant outcomes accordingly. 2) .2) Of the 1861 eligible patients across the entire study period, medical records were unavailable for 57 patients(3.6%)[17(2.4%) from the preintervention cohort and 40(3.7%) from the postintervention cohort.]	Low risk of bias: all primary and secondary outcomes were reported completely.	High risk of Bias:"attitudes and beliefs" or leadership style may have affected the success uptake of the intervention.
Fagerberg B et al,2000, Sweden	Low risk of Bias: randomized the patients by opening a serially numbered sealed envopled	Uncertainty:insufficient information about the sequence generation process to permit judgement.	High risk of Bias: the internist or neurologist on call conduct the patient randomization.	Low risk of bias: Only 7 out of 83 patients did not complete the follow-up in control branch. Only 6 out of 166 patient were missing in follow-up in intervention group.	Low risk of bias: all primary and secondary outcomes were reported completely.	High risk of bias: Different degrees of severity of stroke among the studied patients may influence the results, since such patients constituted a minority and the favorable effect may have been overshadowed by the patients with less severe stroke. .
Panella M et al,2012, Italy	Low risk of bias: patient randomization was carried out using a computer-generated sequence	Low risk of bias: the randomization works with allocation concealment	High risk of bias: 1) the selection of units and the final randomization was based on the comparability of their location, patient population and volume, facilities and teaching status. 2) Blinding of patients and clinicians was not possible (Hawthorne effect).	Uncertainty: insufficient reporting of attrition/exclusions to permit judgement	Low risk of Bias: all primary and secondary outcomes were reported completely.	High risk of bias:1) Selection bias may have occurred both at the individual and cluster levels;2) CPs used in the study were not completely identical because of organizational adaptions at some sites.

Sulch D et al,2000, UK	Low risk of bias: on the basis of a computer-generated list of random number	Low risk of bias: the responsible physician called the randomization office, which conformed eligibility and allocation independently.	Low risk of Bias: No blinding of service providers is less likely to introduce the bias.	Low risk of bias: 1) the rates of incomplete records were lower than 12%;	Low risk of bias:all of the pre-defined outcomes (primary and secondary) that are of interest in the study have been reported in the pre-specified way.	Low risk of Bias: 1) three-month piloting was conducted in advance to reduce the practice bias.2) Crossover of intervention s was minimized by using 2 different teams in 2 different wards areas to implement the 2 different strategies.
Torp CR et al,2006,Denmark	Low risk of Bias: cluster allocation with computer-generated random number	High risk of bias: patients were prerandomized according to address	Low risk of bias: A concealed randomization was impossible as intervention contained close contact to the patients. Comparison of baseline data showed that the randomization was successful.	Low risk of Bias: the 37 out of 410 patients were not examined attributable to clerical errors. But the comparison of the excluded and included patients showed no significant differences regarding age and gender.	Low risk of bias:all of the pre-defined outcomes (primary and secondary) that are of interest in the study have been reported in the pre-specified way.	Uncertainty: 1) the term “standard aftercare” conceals many different treatment and rehabilitation programs. The effects of some standard aftercare are clearly underestimated and not comparable.2)Although the groups were rather comparable at baseline, it of course cannot be ruled out that the lack of effect could be attributable to unknown confounding.

Appendix C

C1:Histogram of selected variables

Age

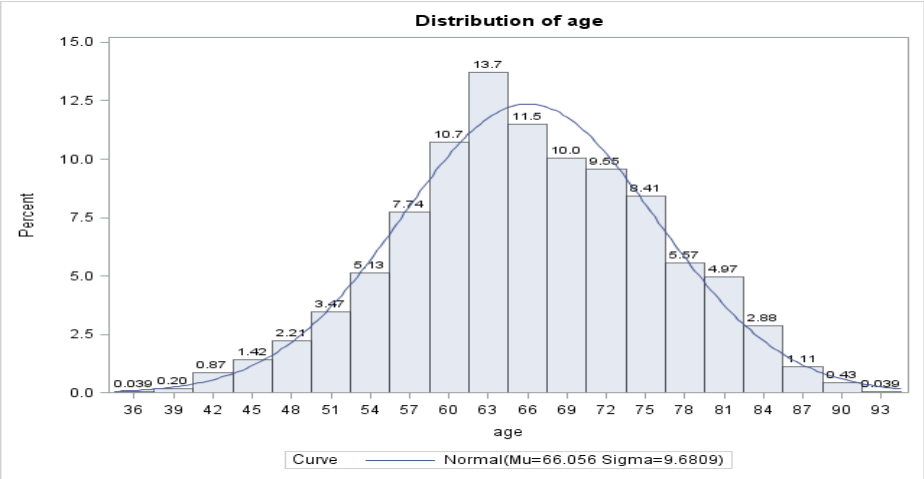

Figure C1-1 Distribution of age for general patient cohort

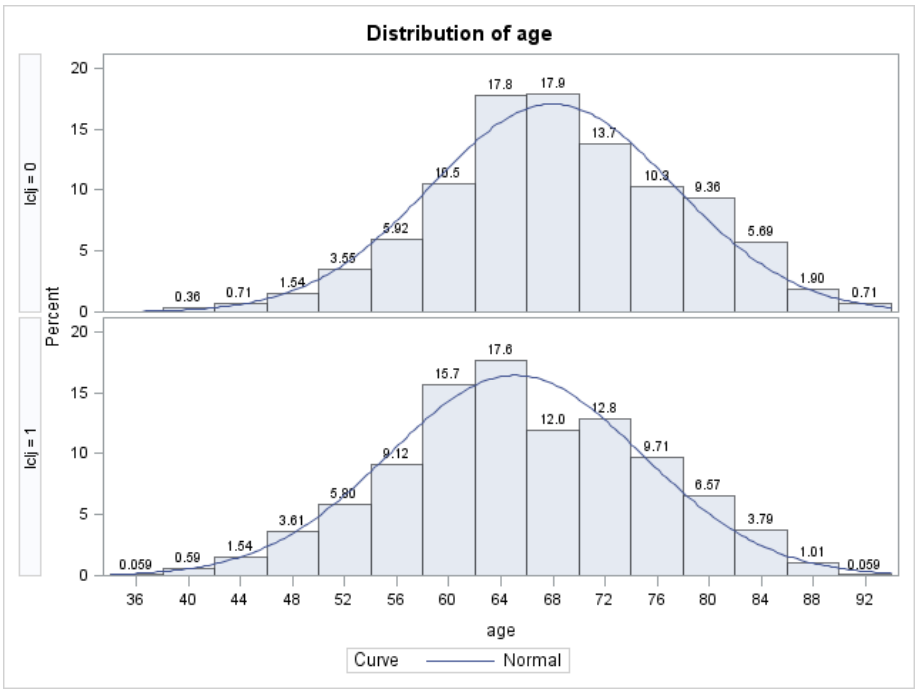

Figure C1-2 Distribution of age for control arm (upper) and treatment arm (lower)

The histogram of age in general group of patients appears to be a normal distribution, with one clear center that the data are clustered around. Around 95% of

the values lie within two standard deviations of the mean value of 66.06 years old. In the control arm, the histogram appears to be a roughly normal distribution roughly with the center value of 67.97 years old. In the treatment arm, the similar trend was observed, with a slightly higher frequency around 64 years old.

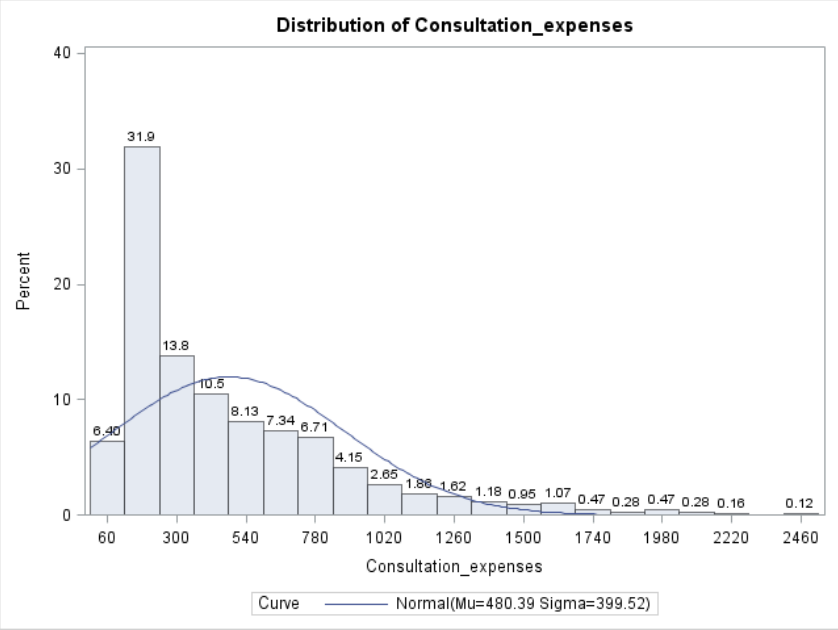

Figure C1-3 Distribution of consultation expenses (YUAN)for general patient cohort

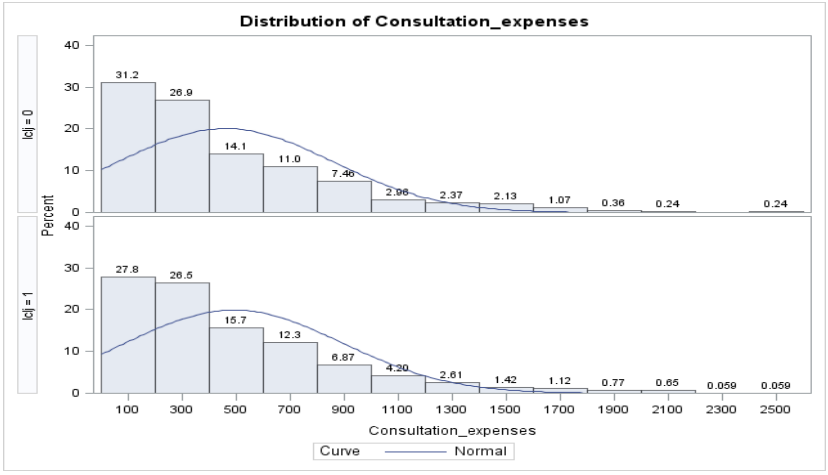

Figure C1-4 Distribution of consultation expenses (YUAN)for control arm (upper) and treatment arm (lower)

The histogram of consultation expenses in general group of patients appears to be a skewed right distribution, in which the tail on the right side of the histogram is longer than the left side. This means the data is generally clustered around a small mean value of 480.39YUAN and larger values are fewer. In the control arm, the histograms appear to be skewed right distribution as well with a continuously decreasing tendency along the x-axis. In the treatment arm, a similar trend was observed, with a higher frequency around 100 YUAN.

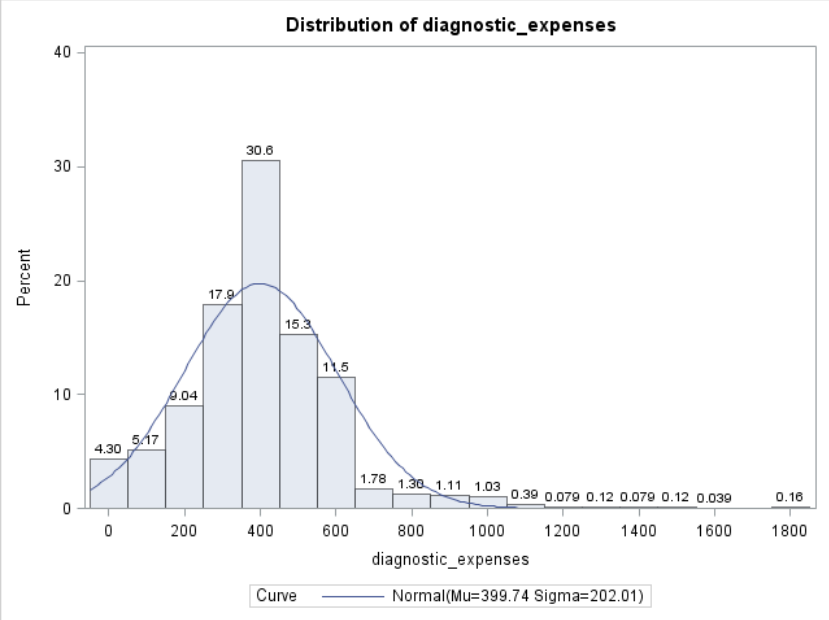

Figure C1-5 Distribution of diagnostic expenses (YUAN) for general patient cohort

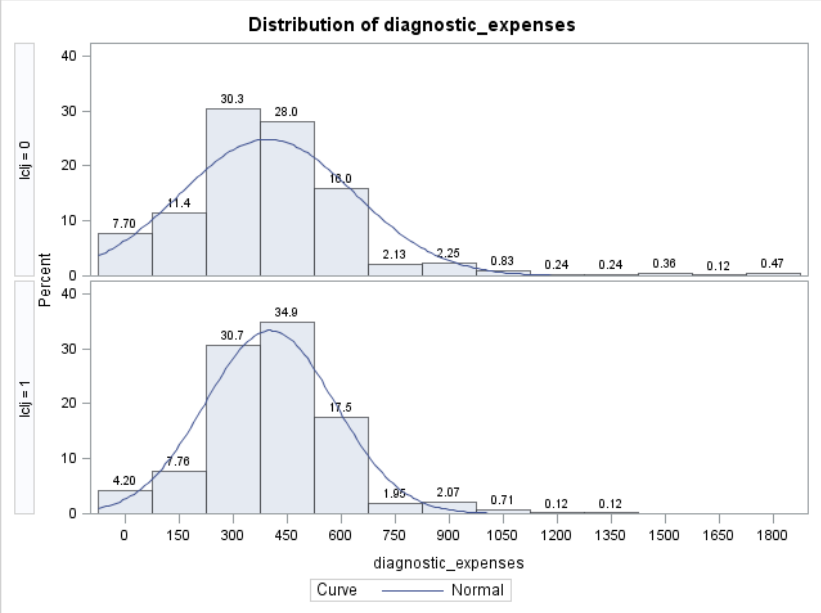

Figure C1-6 Distribution of diagnostic expenses (YUAN)for control arm (upper) and treatment arm (lower)

The histogram of diagnostic expenses in general group of patients appears to be a skewed right distribution, in which the tail on the right side of the histogram is longer than the left side. This means the data is generally clustered around a small mean value of 399.74 YUAN and larger values are fewer. In the control arm, the histograms appear to be skewed right distribution as well with the decreasing tendency along the increased value on x-axis. In the treatment arm, the similar trend was observed, but the values around 450YUAN accounts for a relative higher frequency.

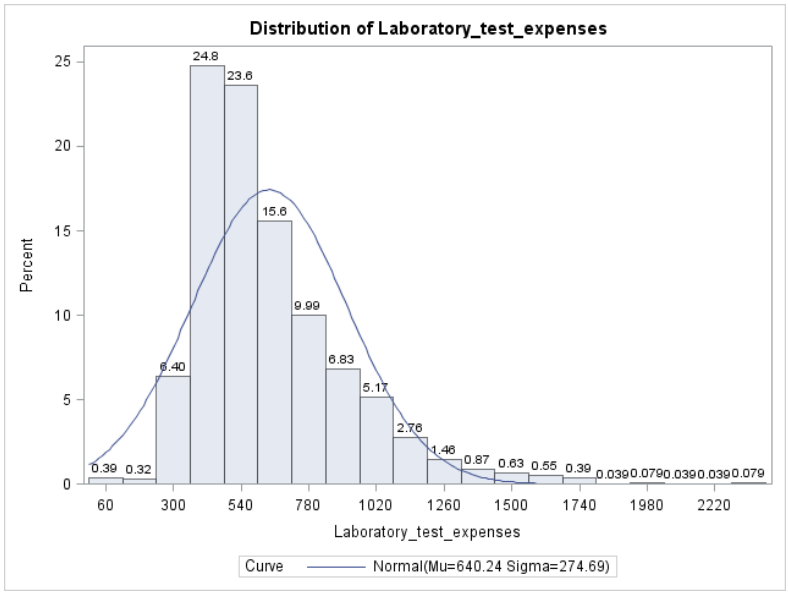

Figure C1-7 Distribution of laboratory test expenses (YUAN) for general patient cohort

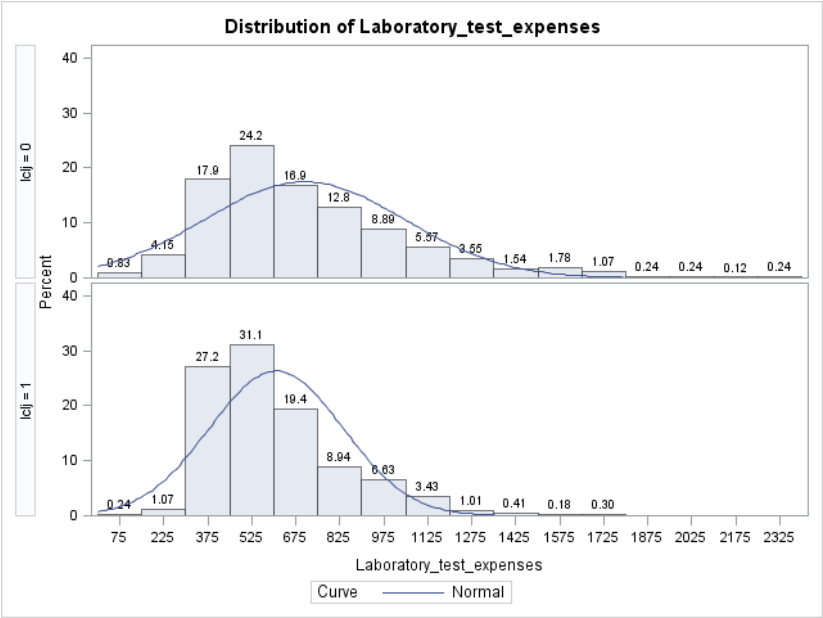

Figure C1-8 Distribution of laboratory test expenses (YUAN)for control arm (upper) and treatment arm (lower)

The histogram of laboratory test expenses in general group of patients appears to be a skewed right distribution, in which the tail on the right side of the histogram is longer than the left side. This means the data is generally clustered around a small mean value of 640.24 YUAN and larger values are fewer. In the control arm, the

histograms appear to be skewed right distribution as well with the decreasing tendency along the increased value on x-axis. In treatment arm, the similar trend was observed, but the values around 525YUAN accounts for a relative higher frequency.

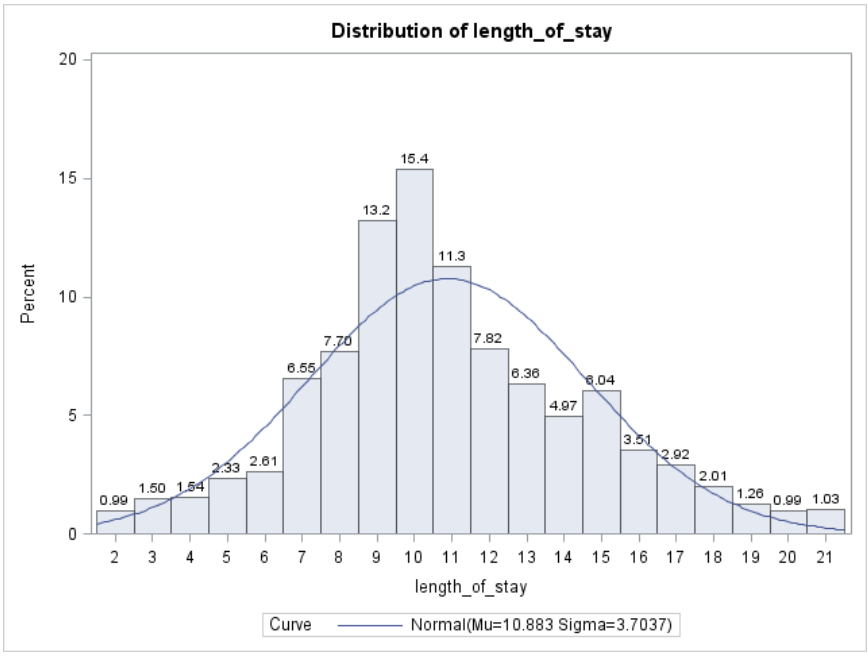

Figure C1-9 Distribution of LOS (DAY) for general patient cohort

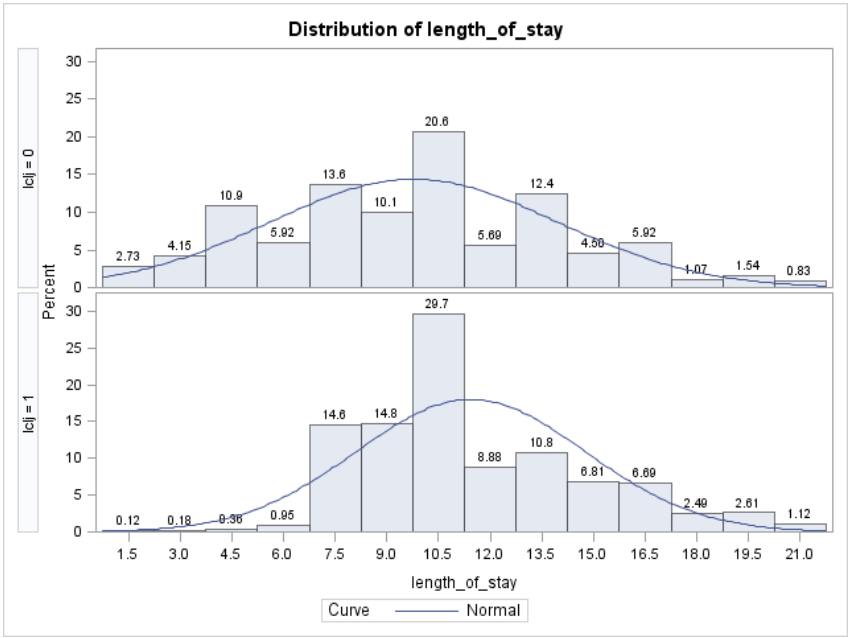

Figure C1-10 Distribution of LOS (DAY)for control arm (upper) and treatment arm (lower)

The histogram of LOS in general group of patients appears to be a normal distribution, with one clear center that the data are clustered around. Around 95% of the values lied within two standard deviations away from mean value of 10.88days, while the more extreme values on either side of the center become less rare as the distance from the peak center. In control arm, the histogram appears to be an approximate normal distribution with the center value of 10.5 days, but the frequency trend seems fluctuated. In treatment arm, the skewed right distribution was observed in which the tail on the right side of the histogram is longer than the left side, and the larger values tends to decrease in a bigger range on x-axis.

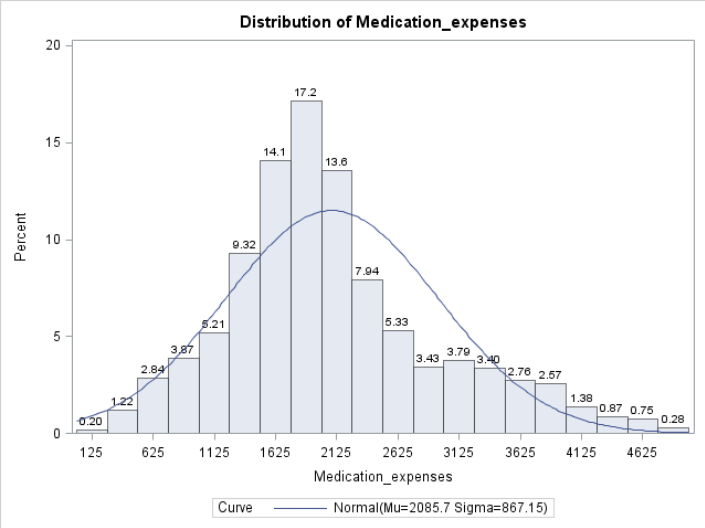

Figure C1-11 Distribution of medication expenses (YUAN) for general patient cohort

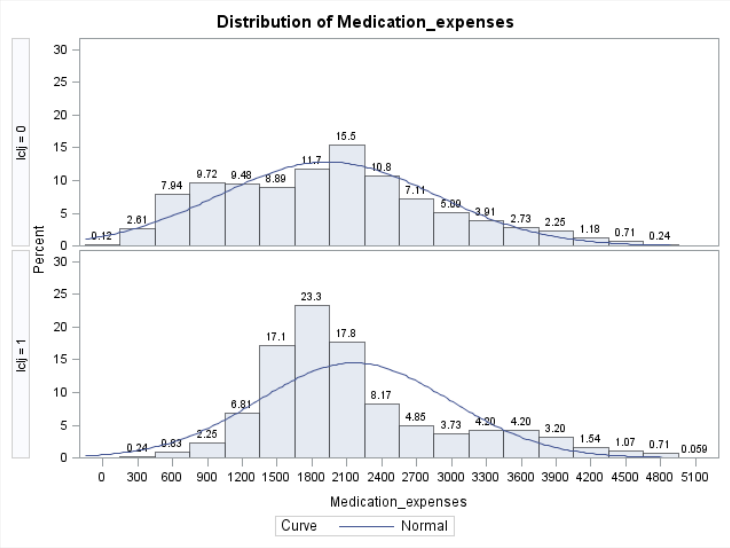

Figure C1-12 Distribution of medication expenses (YUAN)for control arm (upper) and treatment arm (lower)

The histogram of medication expenses in general group of patients appears to be a proximate normal distribution, with one clear center that the data are clustered around. Around 95% of the values lied within two standard deviations away from mean value of2085.70YUAN, while the more extreme values on either side of the center become less rare as the distance from the peak center. Visually, the histogram appears to be a skewed right distribution, in which the tail on the right side of the histogram is longer than the left side, and the larger values are fewer in right tail. In the control arm, the histogram states a light skewed right distribution, where the left side of distribution follows an apparent uniform pattern has approximately the similar number of values in each frequency group. In the treatment arm, an obvious skewed right distribution was observed.

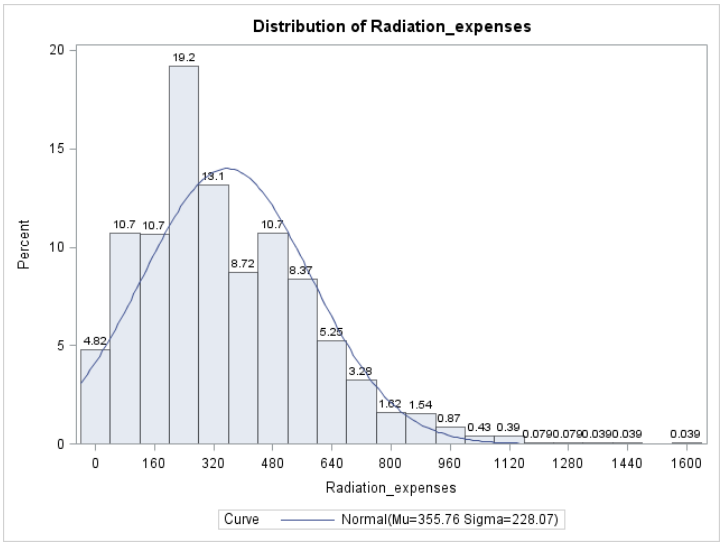

Figure C1-13 Distribution of radiology expenses (YUAN) for general patient cohort

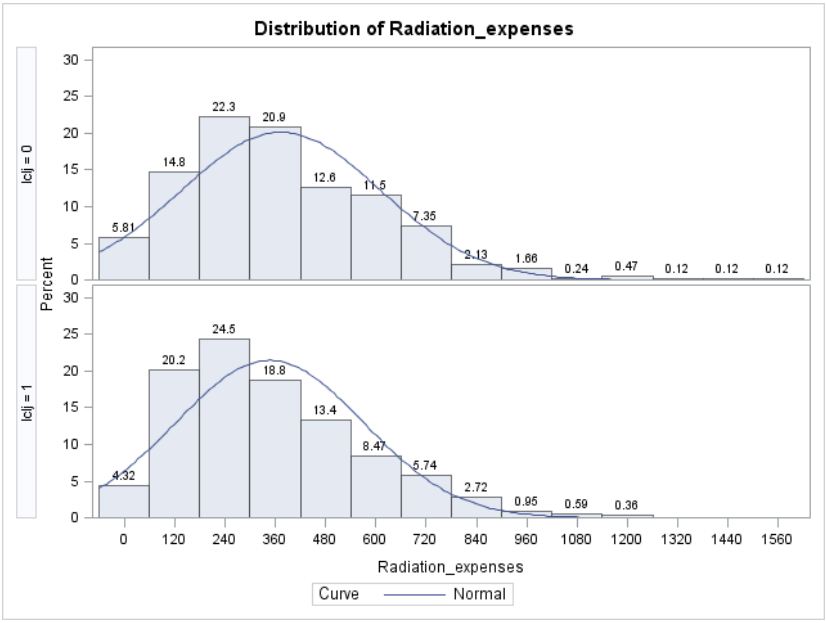

Figure C1-14 Distribution of radiology expenses (YUAN)for control arm (upper) and treatment arm (lower)

The histogram of radiology expenses in general group of patients appears to be a skewed right distribution, in which the tail on the right side of the histogram is longer than the left side. This means the data is generally clustered around a small mean value of 355.76 YUAN and larger values are fewer. In the control arm, the histograms appear to be skewed right distribution as well with the decreasing tendency along the

increased value on x-axis. In treatment arm, the similar trend was observed, but the values around 240YUAN accounts for a relative higher frequency.

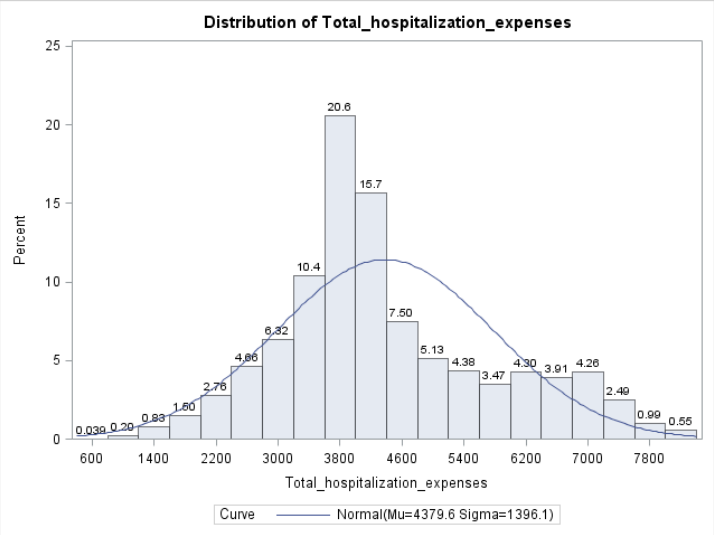

Figure C1-15 Distribution of total hospitalization expenses (YUAN) for general patient cohort

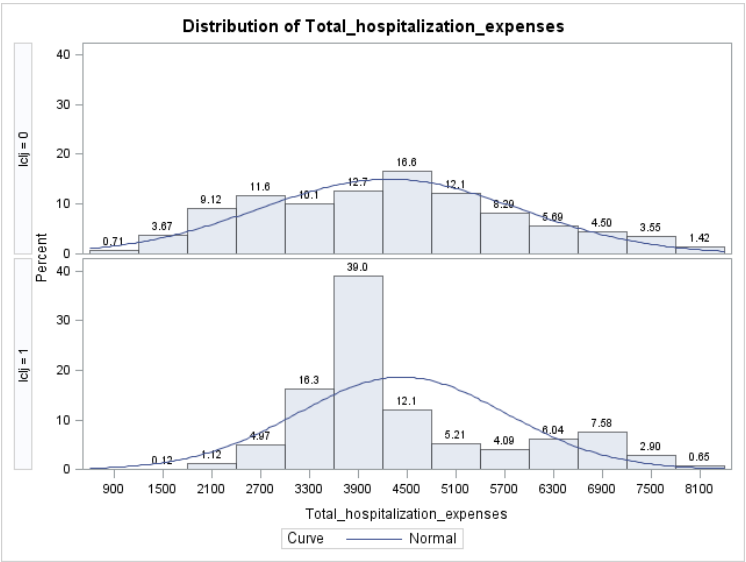

Figure C1-16 Distribution of total hospitalization expenses (YUAN)for control arm (upper) and treatment arm (lower)

The histogram of total hospitalization expenses in general group of patients appears to be a proximate normal distribution, with one clear center that the data are clustered around. Around 95% of the values lie within two standard deviations away

from mean value of 4379.65 YUAN, while the more extreme values on either side of the center become less rare as the distance from the peak center. Visually, the histogram appears to be a light skewed right distribution, in which the tail on the right side of the histogram seems longer than the left side, and the larger values are fewer in right tail. In the control arm, the histogram states a light skewed right distribution, where the left side of distribution follows an apparent uniform pattern has approximately the similar number of values in each frequency group. In the treatment arm, the distribution shape of the data in the histogram is skewed right distribution apparently, and the bi-mode occurs, as there are two peaks for the data item.

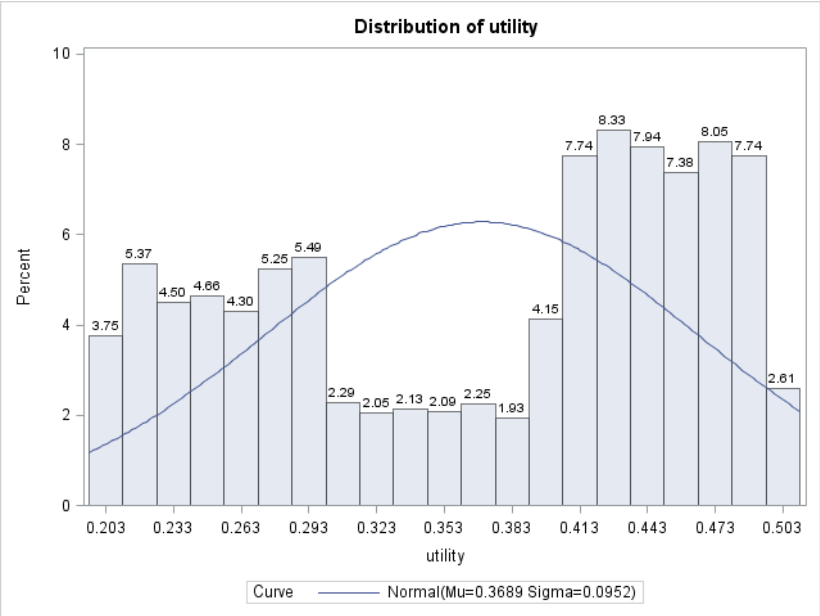

Figure C1-17 Distribution of utility score for general patient cohort

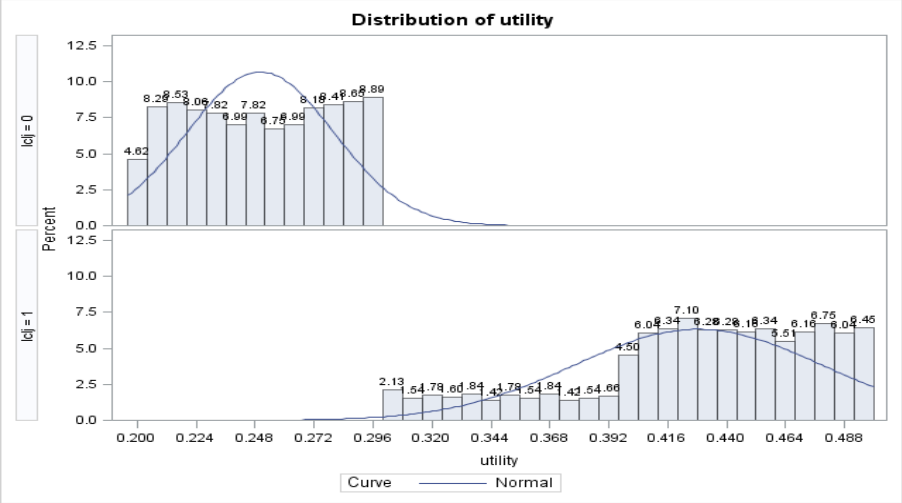

Figure C1-18 Distribution of utility score for control arm (upper) and treatment arm (lower)

The distribution shape of the utility score for general population in the histogram is skewed left distribution slightly, and the bi-mode occurs, as there are two peaks for the data item. The data is generally clustered around a mean value of 0.369 and the higher scores are more than the lower ones. In the control arm, the histograms appear to be skewed right distribution as well with the decreasing tendency along the increased value on x-axis. In treatment arm, a significant skewed left distribution was observed. In addition, we can see that the two-peak distribution for general population can be explained by the two adverse sub groups.

C2: Results of Diagnostic Plots in ITS

Length of Stay

Referring to Figure C2-1, looking at the studentized residuals vs. predicted values, the points appear to be randomly scattered about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be any systematic trend suggesting that independence is met. There appear to be some

outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multi-linear regression are met.

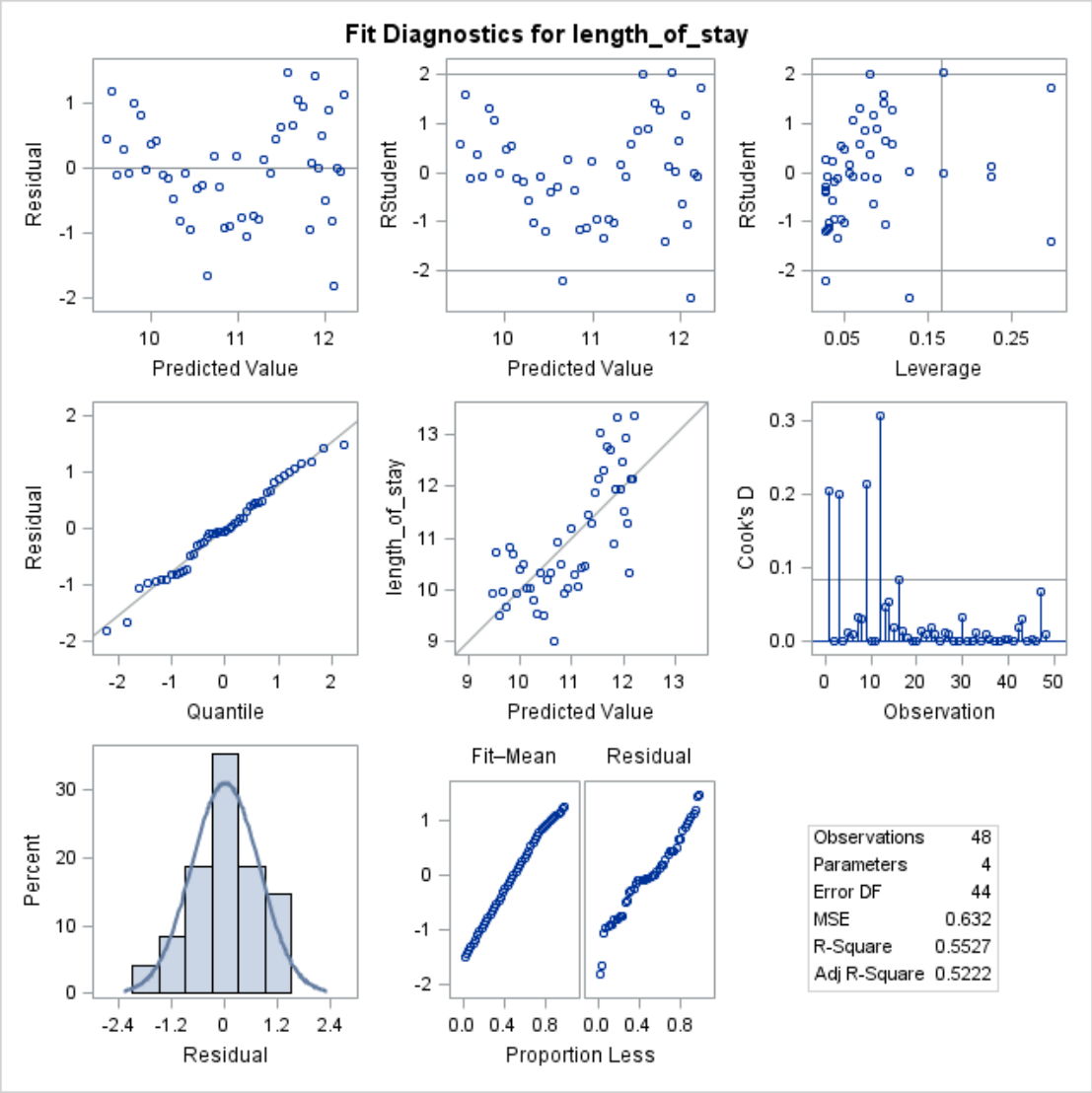

Figure C2-1Diagnostic Plots for LOS

EQ-5D based utility value

Referring to Figure C2-2, looking at the studentized residuals vs. predicted values, the points appear to be randomly scatted about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be any systematic trend suggesting that independence is met. There appear to be some

outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multilinear regression are met.

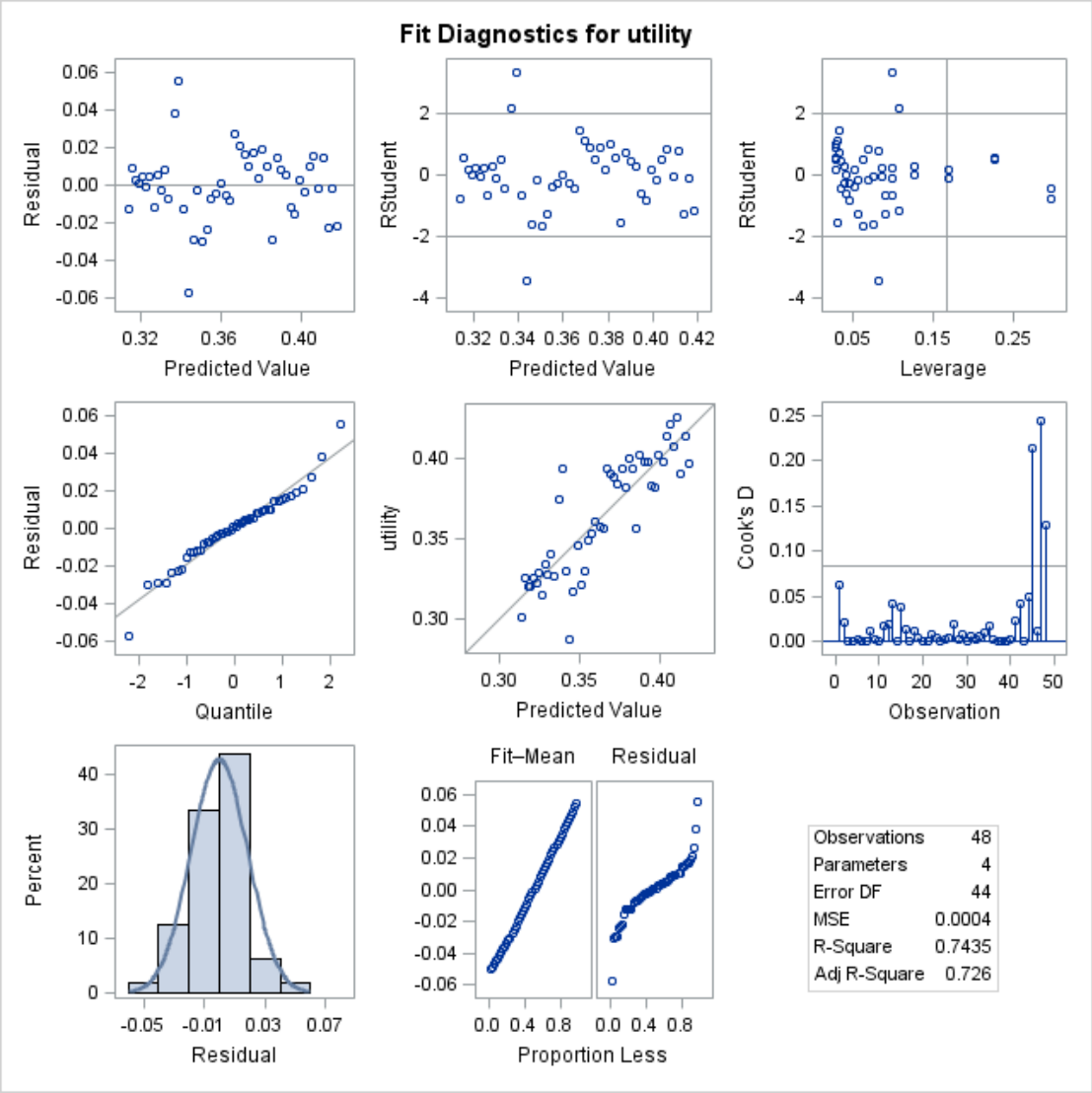

Figure C2-2 Diagnostic Plots for EQ-5D based utility value

Referring to Figure C2-3, looking at the studentized residuals vs. predicted values, the points appear to be randomly scatted about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be any systematic trend suggesting that independence is met. There appear to be some

outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multilinear regression are met.

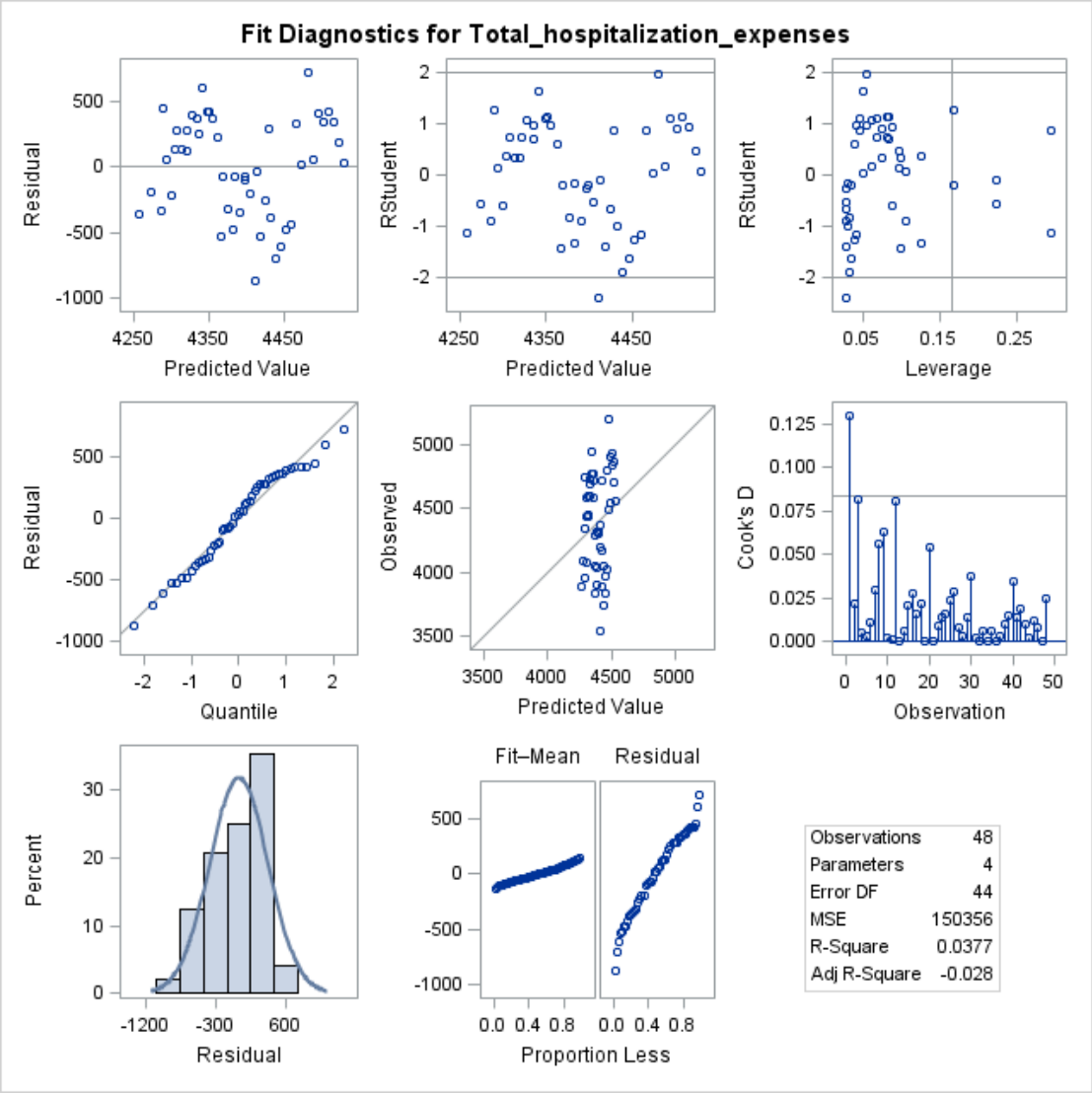

Figure C2-3 Diagnostic Plots for total hospitalization expenses

Medication expenses

Referring to Figure C2-4, looking at the studentized residuals vs. predicted values, the points appear to be randomly scatted about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be

any systematic trend suggesting that independence is met. There appear to be some outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multilinear regression are met.

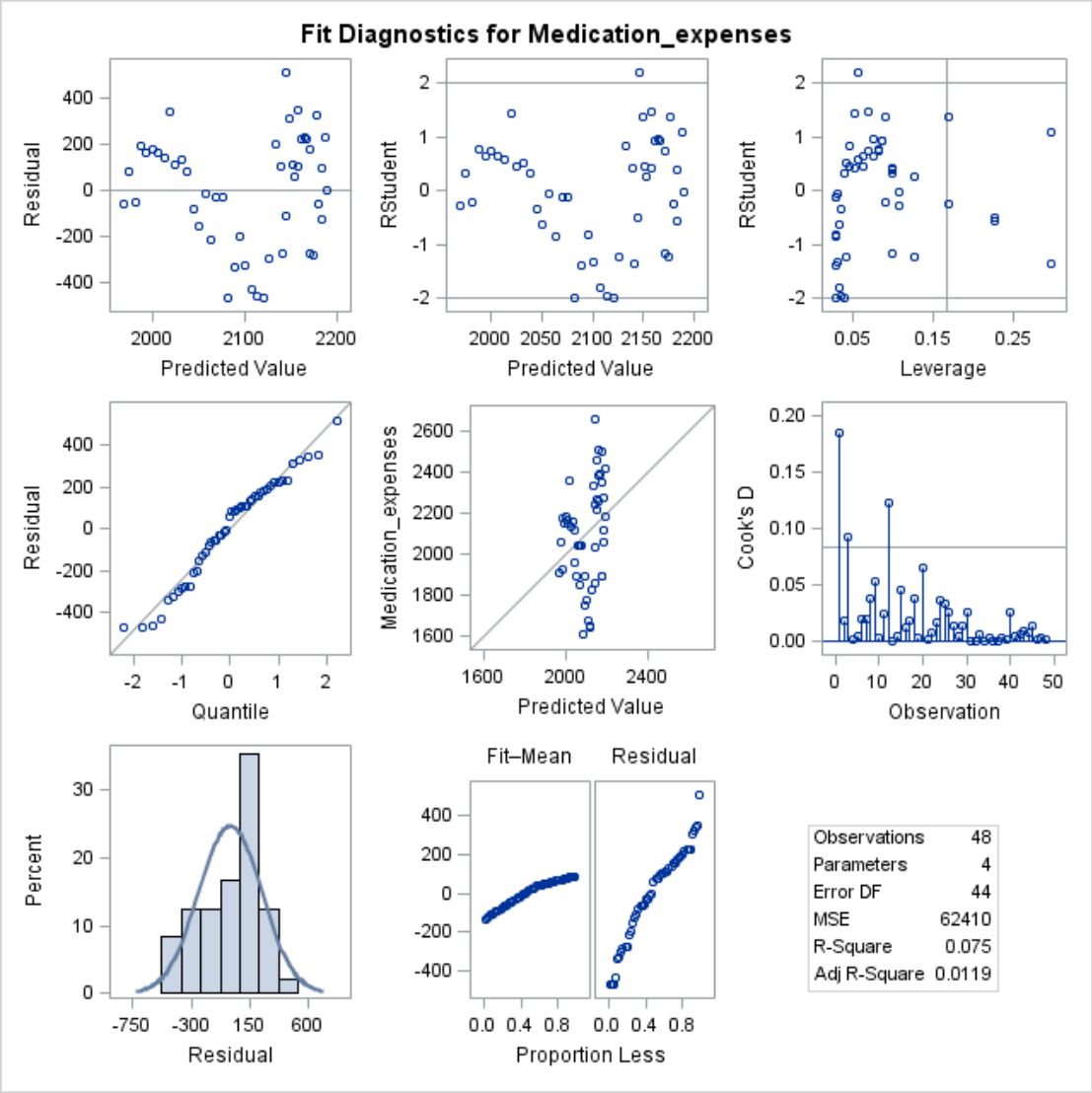

Figure C2-4 Diagnostic Plots for medication expenses

Radiology expenses

Referring to Figure C2-5, looking at the studentized residuals vs. predicted values, the points appear to be randomly scatted about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be

any systematic trend suggesting that independence is met. There appear to be some outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multilinear regression are met.

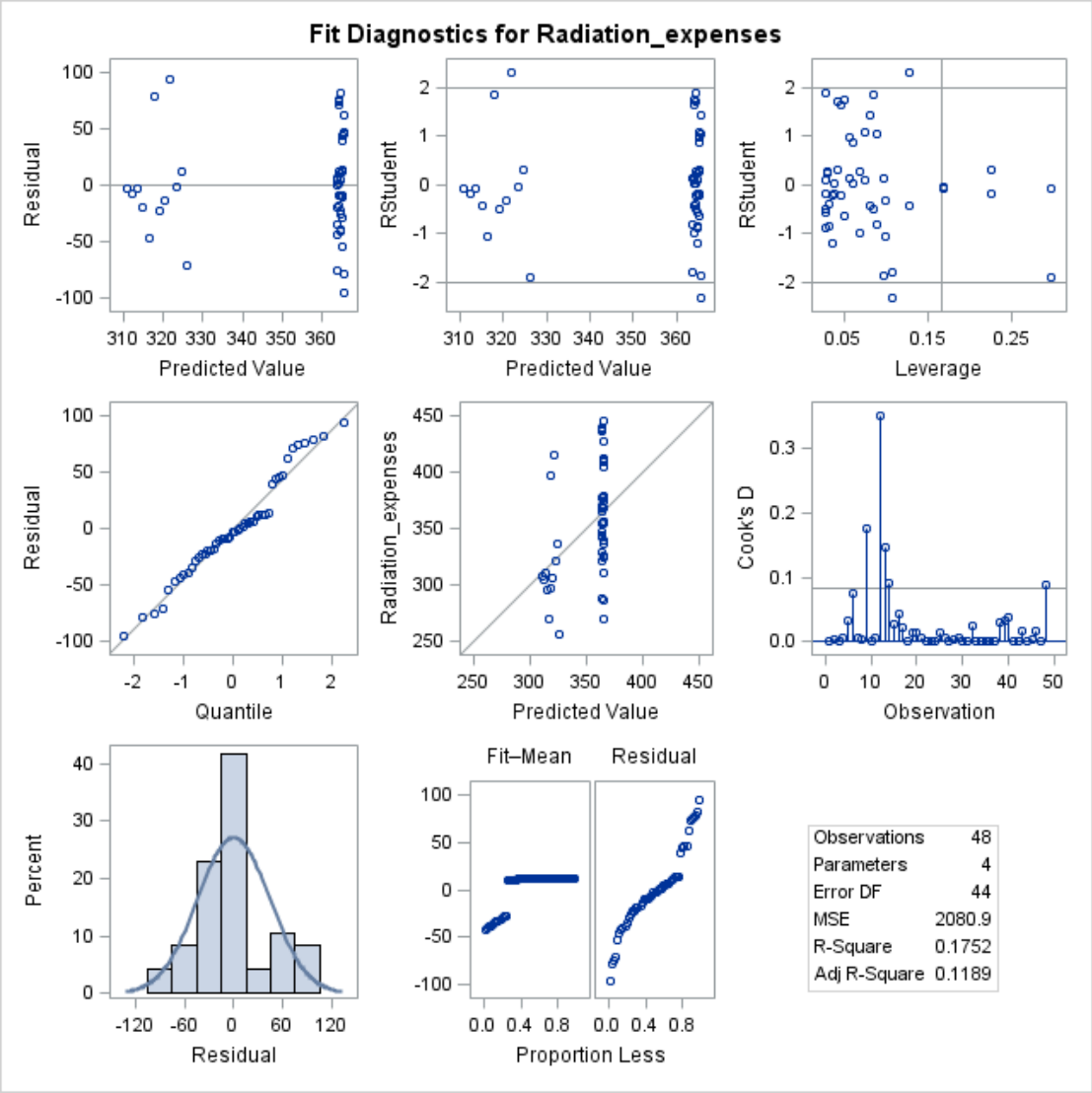

Figure C2-5 Diagnostic Plots for Radiology expenses

Laboratory test expenses

Referring to Figure C2-6, looking at the studentized residuals vs. predicted values, the points appear to be randomly scatted about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be

any systematic trend suggesting that independence is met. There appear to be some outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multilinear regression are met.

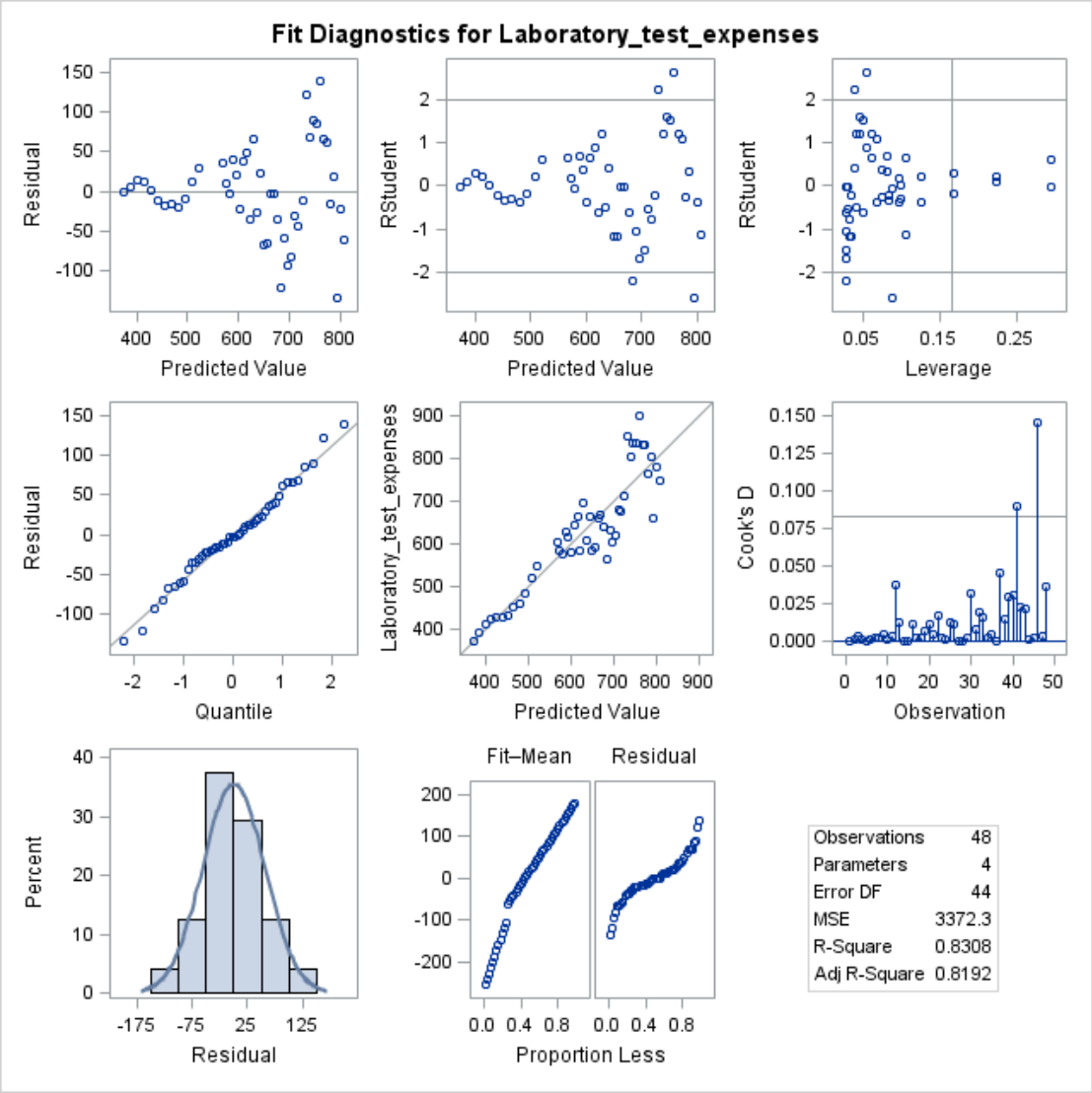

Figure C2-6 Diagnostic Plots for laboratory test expenses

Consultation expenses

Referring to Figure C2-7, looking at the studentized residuals vs. predicted values, the points appear to be randomly scatted about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be

any systematic trend suggesting that independence is met. There appear to be some outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multilinear regression are met.

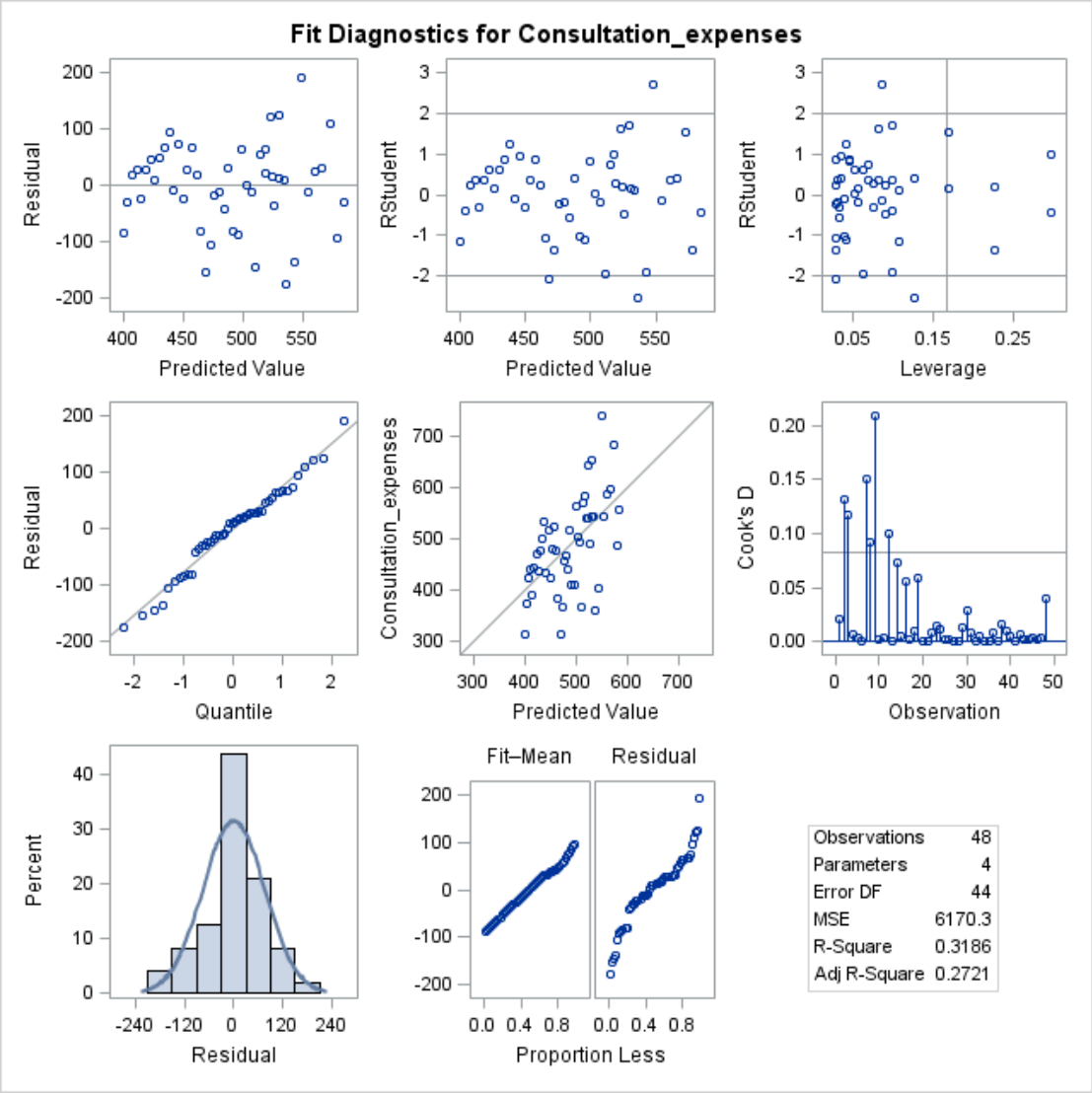

Figure C2-7 Diagnostic Plots for consultation expenses

Diagnostic expenses

Referring to Figure C2-8, looking at the studentized residuals vs. predicted values, the points appear to be randomly scatted about zero, suggesting that mean does equal zero. There appears to be no difference in spread across the residuals, this suggests that the assumption of constant variance is met. There does not appear to be

any systematic trend suggesting that independence is met. There appear to be some outliers, which are highlighted by the leverage and Cook's distance (Cook's D) plots. Generally, the assumptions of multilinear regression are met.

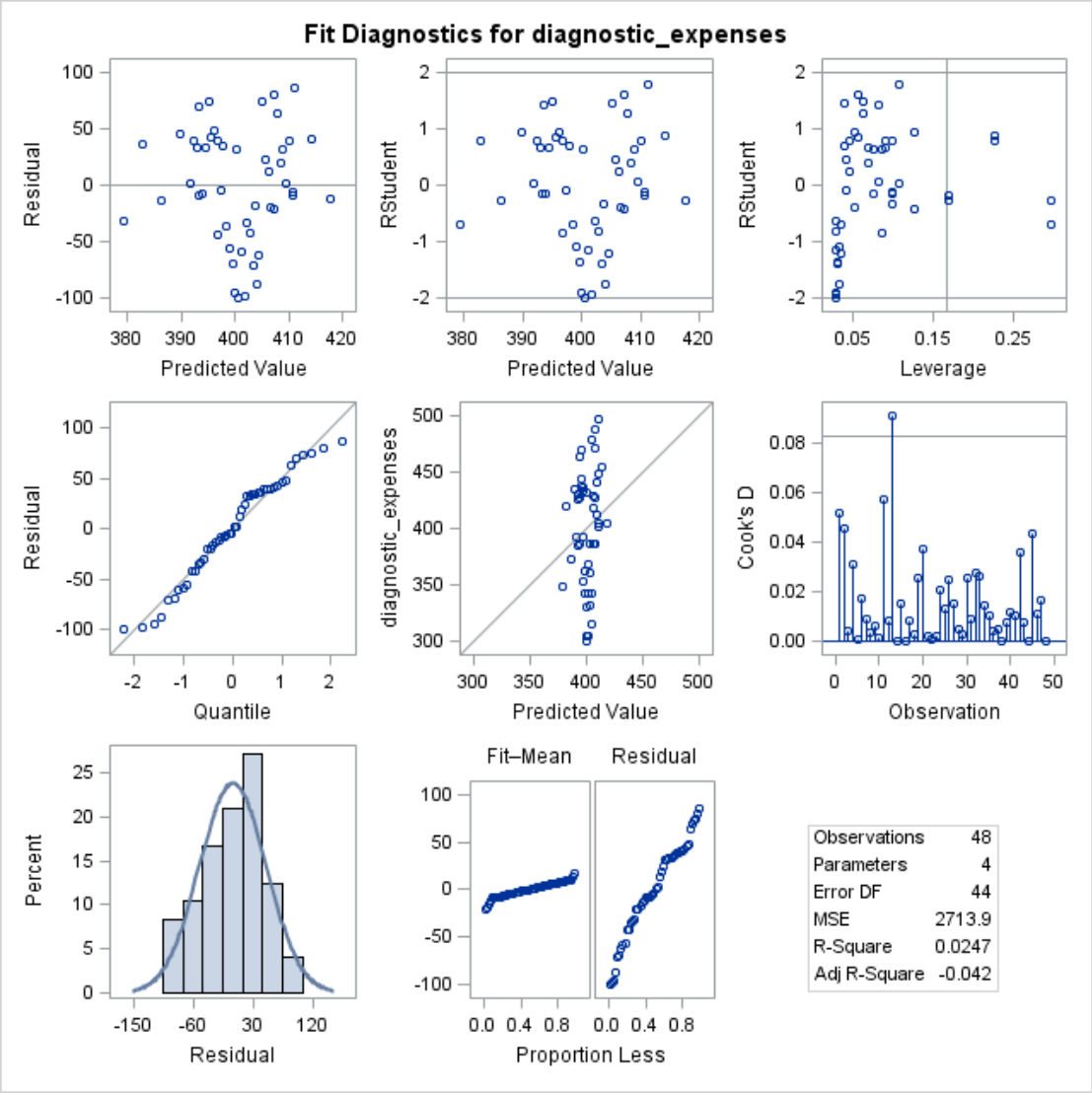

Figure C2-8 Diagnostic Plots for Diagnostic expenses

C3: Transition probabilities between outpatient and inpatient applied in models

Intervention	State	Probability	Cycle	Source
CP	Inpatient to outpatient (Acute stage)	0.000	1	Real-world data
		0.001	2	
		0.003	3	

		0.000	4	
		0.003	5	
		0.010	6	
		0.072	7	
		0.088	8	
		0.156	9	
		0.169	10	
		0.135	11	
		0.086	12	
		0.042	13	
		0.051	14	
		0.082	15	
		0.040	16	
		0.024	17	
		0.013	18	
		0.010	19	
		0.010	20	
		0.000	21	
		0.000	22	
	Outpatient to inpatient	0.157	--	(Tu, 2016)
Non-CP	Inpatient to outpatient (Acute stage)	0.000	1	Real-world data
		0.028	2	
		0.031	3	
		0.049	4	
		0.066	5	
		0.057	6	
		0.067	7	
		0.067	8	
		0.105	9	
		0.166	10	
		0.095	11	
		0.055	12	
		0.082	13	
		0.052	14	
		0.045	15	
		0.041	16	
		0.017	17	
		0.012	18	
		0.007	19	
		0.008	20	

		0.000	21	
		0.000	22	
	Outpatient to inpatient	0.157	--	(Tu, 2016)

C4: Mortality rates used in outpatient at stable stage

State	Mortality	age	Source
Outpatient (Stable stage)	0.008	60	(Statistics, 2015)
	0.007	61	
	0.009	62	
	0.008	63	
	0.009	64	
	0.009	65	
	0.010	66	
	0.013	67	
	0.013	68	
	0.014	69	
	0.015	70	
	0.021	71	
	0.022	72	
	0.024	73	
	0.027	74	
	0.029	75	
	0.034	76	
	0.032	77	
	0.040	78	
	0.041	79	
	0.053	80	
	0.056	81	

C5:Distribution of parameters used in PSA

Parameters	Distribution
A_CP_P_dead_outpatient	beta
A_NCP_P_dead_outpatient	beta
A_CP_P_dead_inpatient	beta
A_NCP_P_dead_inpatient	beta

Parameters	Distribution
A_C_aspi	gamma
A_C_ator	gamma
A_T_aspi	gamma
A_T_ator	gamma
A_Percent_aspi+ator	gamma
A_C_general	gamma
A_C_associate	gamma
A_T_general	gamma
A_T_associate	gamma
A_Percent_general	gamma
A_C_stool	gamma
A_C_sixblood	gamma
A_C_blood	gamma
A_C_urine	gamma
A_C_doppler	gamma
A_C_ct	gamma
A_C_mri	gamma
A_T_stool	gamma
A_T_sixblood	gamma
A_T_blood	gamma
A_T_urine	gamma
A_T_doppler	gamma
A_T_ct	gamma
A_T_mri	gamma
A_Percnet_stool	gamma
A_Percnet_sixblood	gamma
A_Percnet_blood	gamma
A_Percnet_urine	gamma
A_Percnet_doppler	gamma
A_Percnet_ct	gamma
A_Percnet_mri	gamma
A_CP_C_dead	fixed
A_NCP_C_dead	fixed
C_CP_Inpatient_drugs	lognormal
C_CP_Inpatient_radiology	lognormal
C_CP_Inpatient_laboratory	lognormal
C_CP_Inpatient_consultation	lognormal
C_CP_Inpatient_inspection	lognormal
C_NCP_Inpatient_drugs	lognormal
C_NCP_Inpatient_radiology	lognormal

Parameters	Distribution
C_NCP_Inpatient_laboratory	lognormal
C_NCP_Inpatient_consultation	lognormal
C_NCP_Inpatient_inspection	lognormal
Chrionic_CP_C_inpatient	lognormal
Chrionic_NCP_C_inpatient	lognormal
C_CP_C_dead	fixed
C_NCP_C_dead	fixed
C_CP_P_inpatient_outpatient	beta
C_NCP_P_inpatient_outpatient	beta
C_CP_P_dead_inpatient	beta
C_NCP_P_dead_inpatient	beta
U_CP_inpatient（per year）	beta
U_NCP_inpatient（per year）	beta
U_outpatient（per year）	beta
U_dead（per year）	fixed