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Title: Cost-effectiveness of an intervention to improve the quality of nursing care among immobile patients with stroke in China: A multicenter study

Running title: Cost-effectiveness of nursing intervention in immobile stroke patients in China

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Title: Cost-effectiveness of an intervention to improve the quality of nursing care among immobile patients with stroke in China: A multicenter study

Abstract

Background: While a nursing intervention program for immobile patients with stroke can improve clinic outcomes, less is known about the cost-effectiveness of these interventions.

Objectives: The goal of this study was to evaluate the cost-effectiveness of the intervention program for immobile patients with stroke in China.

Design and Setting: This is a pre-test/post-test (before and after) study. Participants were recruited from six provinces or municipal cities in eastern (Guangdong province, Zhejiang province, and Beijing municipal city), western (Sichuan province), and central (Henan province and Hubei province) China.

Participants: A total of 7,653 immobile stroke patients were included in our sample. Patients in routine care settings were recruited from November 2015 to June 2016, and the recruitment of the intervention group patients was from November 2016 to July 2017.

Methods: To adjust for potential bias from confounding variables, the 1:1 propensity score matching yielded matched pairs of 2,966 patients in the routine care group and 2,966 patients in the intervention group, with no significant differences in sociodemographic or clinical characteristics between two groups. All patients were followed-up 3 months after enrolment in the study. Total healthcare costs were extracted from the hospital information system, with the health outcome effectiveness of the intervention program measured using the EuroQol five-dimensional questionnaire (EQ-5D) instrument and the cost-effectiveness of the intervention measured by the incremental cost-effectiveness ratio with a time horizon of 3 months.

Results: Compared to routine care, the intervention program decreased the total costs of stroke patients by CN¥4,600 (95% confidence interval [CI]: [-7050, -2151]), while increasing quality-adjusted life year 0.009 (95% CI: [0.005, 0.013]). The incremental cost-effectiveness ratios over 3 months was CN¥--517,011 per quality-adjusted life year

(95% CI: [-1111442, -203912]). Subgroup analysis reveals that both the health-related quality of life and cost effectiveness improved significantly for ischemic patients and tertiary hospitals patients while for hemorrhagic patients and non-tertiary hospital patients only the health-related quality of life improved significantly.

Conclusions: Findings from this first cost-effectiveness analysis in immobile stroke patients provide evidence that an intervention program provided significant cost saving, but mainly in ischemic patients and tertiary hospital patients. Wider adoption of such programs may be a sensible approach to reducing the burden of stroke and for immobile patients more generally.

What is already known about the topic?

- Medical complications after stroke can increase the costs of health care and account for a significant part of direct costs of stroke.
- A nursing intervention program can decrease the incidences of medical complications (such as pressure injuries, pneumonia, deep vein thrombosis, and urinary tract infections), less is known about the cost-effectiveness of these interventions.
- Few cost-effectiveness analyses of nursing interventions for immobile stroke patients have been undertaken in China.

What this paper adds

- A nursing intervention program for immobile stroke patients can save costs and are also more effective in health-related quality of life outcomes for immobile stroke patients than routine care.

- Both the health-related quality of life and cost effectiveness improved significantly for ischemic patients and in tertiary hospitals while for hemorrhagic patients and in non-tertiary hospitals only the health-related quality of life improved significantly.
- This is the first study to compare the costs and effects of implementing a nursing intervention program on immobile stroke patients, providing a realistic picture of the health benefits that could be achieved if this program were implemented on a nationwide scale.

Key words: Cost-effectiveness; Cost-utility analysis; Costs and cost analysis; Nursing; Stroke; Health-related quality of life; Propensity score; Predictive mean matching; Multicenter study

1. Introduction

Stroke is the second leading cause of death and disability worldwide (Hankey, 2017, Wu et al., 2019), levying high annual costs on hospitals, the health system and the society (Kim et al., 2015). It is estimated that €64.1 billion is spent yearly on stroke in Europe (Feigin et al., 2015), of which about two-thirds is for direct stroke health care costs (Feigin et al., 2015). Accounting for about one-third of global deaths from stroke (Feigin et al., 2015), China's 2.5 million annual new strokes victims and 7.5 million stroke survivors (Johnston et al., 2009, Liu et al., 2011), impose significant costs on China's health system. Stroke survivors are frequently made immobile, suffering medical complications (Kumar et al., 2010) such as pressure injuries (McGillivray and Considine, 2009, Pandian et al., 2012, Sackley et al., 2008, Theofanidis and Gibbon, 2016), pneumonia (Kumar et al., 2010, McGillivray and Considine, 2009, Sidhartha et al., 2015), deep vein thrombosis (Kumar et al., 2010, Shah et al., 2015, Sidhartha et al., 2015) and urinary tract infections (Pandian et al., 2012, Sidhartha et al., 2015, Yan et al., 2018). These stroke-related complications may severely hinder the functional recovery of stroke patients, resulting in poorer final recovery outcomes, increasing the length of hospital stays and decreasing patient's quality of life (Kumar et al., 2010). They impose significant costs on China's health care system.

Previous studies indicate that complications after stroke can increase the costs of health care and account for a significant part of direct costs of stroke (Demaerschalk et al., 2010, Joo et al., 2014, Kumar et al., 2010, Navarrete-Navarro et al., 2007, Sackley et al., 2008). In 2017 for example, the cost per hospitalization for ischemic stroke was

CN¥10,131, while China's per capita disposable income was CN¥25,974 (Yong et al., 2018). Currently, the direct costs for stroke treatment in China is about CN¥37.5 billion annually, or CN¥50 billion when indirect costs are included (Wu et al., 2015). For patients immobilized by stroke, the cost of stroke care due to medical complications may increase the economic burden of stroke (Liu et al., 2011, Westendorp et al., 2018).

But, with timely assessment and standardized nursing care, such as general body support, physiological surveillance and early mobilization, many of these complications are preventable or the adverse outcomes ameliorated (Bae et al., 2005, Johnston et al., 1998, Langhorne et al., 2000, McGillivray and Considine, 2009). Some randomized controlled trials (RCTs) have shown that standardized and integrated nursing care may lead to better outcomes in the acute phase of stroke care (Indredavik et al., 2000, Sinha and Warburton, 2000, Sulch et al., 2002) and several investigators have shown that standardized nursing interventions can reduce the frequency of stroke complications, decrease stroke health care costs and improve the health-related quality of life of immobile stroke patients (Anthony, 2013, Balami et al., 2011, Granitto and Galitz, 2008, Lombard et al., 2009, Miller, 2016, Quinn et al., 2014).

Surprisingly, few cost-effectiveness analyses of nursing interventions for immobile stroke patients have been undertaken in China. Supported by National Health and Family Planning Commission's agenda to improve the quality of nursing care and clinical outcomes among immobile patients, our study developed a standardized nursing intervention program for immobile patients with four major immobility complications: pressure injuries, deep vein thrombosis, pneumonia and urinary tract infections. Training in our intervention program was conducted in 25 hospitals from six provinces or municipal cities in China (Eastern: Guangdong province, Zhejiang province, Beijing municipal city; Western: Sichuan province; and Central China: Henan province and Hubei province), comprising six tertiary hospitals, 11 secondary hospitals and eight community hospitals.

Our previously study found that compared with routine nursing care, the intervention program decreased the incidences of major immobility complications and improved clinical outcomes in immobile patients (Liu et al., 2019, Wu et al., 2018), but did not evaluate the cost-effectiveness of routine versus intervention care. Taking a health care perspective, we used the propensity score matching statistical technique and cost-utility analysis to investigate whether implementing an intervention program can both improve the health-related quality of life and save health care costs for immobile stroke patients. Specifically, we test whether hemorrhagic and ischemic stroke might be prone to different complications (Ali et al., 2009, Bae et al., 2005, Dennis et al., 2016, Kong et al., 2016, Kumar et al., 2010, Liu et al., 2018) with different health care cost effectiveness implications. We also test whether there were significant differences in nursing care costs effectiveness between tertiary and non-tertiary hospitals (Liu et al., 2019).

2. Methods

2.1. Study design and participants

Our study design is a pre-test/post-test (before and after) study, comparing immobile patients with ischemic and hemorrhagic stroke in the intervention group versus routine care group from 25 hospitals in China between November 2015 and July 2017. For the routine care group, 3,891 patients were recruited from November 2015 to June 2016, and for the intervention group, 3,762 patients were recruitment from November 2016 to July 2017. All patients were followed-up 3 months after enrolment in the study.

Between November 2015 and June 2016, we developed the intervention program based on baseline data (such as the frequency of complications in immobile stroke patients, nursing interventions being implemented for stroke and complications), evidence-based results, and expert opinions. The intervention program contains enhanced nursing practices that reflect specific knowledge and skills, such as risk factors assessment, observation, nursing precaution, nursing intervention, and nursing operations. Details of the intervention program design, the characteristics, training information, and process of data collection are describe in the Supplemental On-line Information).

At 25 hospitals, data on all immobile patients suffering ischemic and hemorrhagic stroke between November 2015 and July 2017 were analyzed. Inclusion criteria comprised being immobile, for at least 24 hours after admission, defined as patients' basic physiological needs being carried out in bed except for active or passive bedside sitting/standing/wheelchair use for examination; granting informed consent; older than 18 years; and diagnosed with ischemic or hemorrhagic stroke. Exclusion criterion was patients with major immobility complication at the time of enrolment.

Using an individual case report form (CRF) from time of enrolment, two pre-trained registered nurses in each ward collected data on patients' socio-demographic characteristics (age, sex, education level, health behavior, insurance type, and region), frequency of major immobility complications and nursing interventions implemented for stroke and major immobility complications. Data collected by nurses were checked daily by the head nurse, including for missing data, to provide validity checks. Costs were derived from the hospital information system (HIS) in each hospital after the enrolled patients were discharged from the hospital, and their health-related quality of life information was gathered 3 months after enrollment using the three-level EuroQol five-dimensional questionnaire (EQ-5D), a standardized instrument for measuring health status, through telephone follow-ups (Golicki et al., 2015), unless they died in hospital or withdrew from medical treatment.

In the final analysis, 7,653 patients were included in our sample. There were 378 (4.94%) patients who died; 575 (7.51%) patients withdrew from treatment; and 224 (2.93%) patients were missing hospital cost data. The study was ethically approved by the authorities of the 25 cooperating hospitals and participants signed a written informed consent before enrolment. For patients with aphasia to consent, consent was signed by a family member.

2.2. Costs and Utility Values

The economic evaluation was conducted from a health care perspective with a 3 month time horizon, meaning that only direct costs within the health care sector were included, and were discounted at a rate of 3% per annum (Ma et al., 2015, Wang et al., 2019, Yang et al., 2012). The China Health Statistics Yearbook indicated that the price index was 2.7 in 2015, and the price index was 3.5 in 2016, the average of the two years of the price index is 3.1, therefore, it was reasonable to choose a discount rate of 3% in the present study. Widely used in economic evaluations of stroke disease (Hunter et al., 2018, Westendorp et al., 2018), cost-effective analysis, a variant of cost-utility analysis, combines the incremental utilities expressed in the unit of quality-adjusted life years (QALYs) gained by a certain intervention with the costs produced by that intervention (Angevine and Berven, 2014). Effectiveness of the intervention program was measured by the EQ-5D index, a standardized instrument for measuring generic health status, comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression on a three-point scale (no/some/extreme problems). EQ-5D generates preference-based scores for health-related quality of life that was used to calculate quality-adjusted life years (Golicki et al., 2015). A literature review revealed that the EQ-5D appears to be appropriately responsive in stroke patients (Golicki et al., 2015), therefore, we considered the progression of EQ-5D scores during the 3-month follow-up period. EQ-5D responses were then valued using population preferences in China (Liu et al., 2014). Cost-effectiveness was measured using the incremental cost-effectiveness ratio (ICER), which is the ratio of the difference in mean cost between intervention group and the routine care group and the difference in their mean effect (Postmus et al., 2011). In cost-utility analysis, it represents the average incremental cost associated with per quality-adjusted life year gained. If the incremental cost per effectiveness is less than 0, the intervention can save costs while achieving health benefit, and if it is less than gross domestic product (GDP) per capita, the intervention can be regarded as highly cost-effective, and it can be regarded as cost-effective if the incremental cost-effectiveness ratio is not more than 3 times the GDP per capita (Wang et al., 2019, Who, 2001, Yang et al., 2012). This approach has already been used in several economic evaluations in many developing countries, including China (Ma et al., 2015, Rachapelle et al., 2013, Xie and Vondeling, 2008, Yang et al., 2012).The GDP per capita for China in 2016 was CN¥53,980; we used CN¥53,980 per quality-adjusted life year as the threshold ratio of willingness to pay (WTP) to determine whether the interventions were cost-effective or not.

2.3. Statistical analysis

To adjust for potential bias from confounding variables, we match the two groups of patients according to their characteristics and facility characteristics. Patients in the routine care group were matched 1:1 to patients in the intervention group by the propensity score using the greedy matching algorithm. We derived the propensity score from a logistic regression model with the following variables: age, sex, education level, smoking, insurance, region, level of hospital, bed time, experience of intensive care unit (ICU), experience of surgery, respiratory invasive operation within one month, tracheotomy within one month, urethral invasive operation within one month and number of Charlson comorbidities (Bar and Hemphill, 2011). Region and level of hospital refer to the provider/facility characteristics in the present study. When all propensity score matches were performed, we assessed the balance in baseline covariates between the two groups using the $\chi 2$ test.

Sample exclusion due to missing values may be sources of bias, if the missing values are not random. To address this concern, we investigated whether the missing sample are different from those non-missing data (see Supplementary Table 2). We found significant differences in some variables between those with and without data. Therefore, to reduce the potential bias of missing data, we replaced missing values for cost and effect data with 10 imputed values using multiple imputation by chained equations (MICE) with predictive mean matching (PMM) (Faria et al., 2014, White et al., 2011). Then we used a mixed effects model to allow for the correlation between measurements over hospitals; a log link function with a gamma distribution for the costs; and an identity function with a Gaussian distribution for health-related quality of life.

2.4. Uncertainty

We created 5,000 bootstrapped replications by drawing 500 samples of the same size as the original samples with replacement from each of the 10 imputations to compute 5,000 bootstrap replication of the cost-effectiveness ratio and then plotted the corresponding cost-effectiveness plane and cost effectiveness acceptability curves (Fenwick et al., 2004, Westendorp et al., 2018). The cost-effectiveness plane shows differences in costs in the Y-axis and differences in effect on the X-axis. Results of bootstrapping are reported with quadrants of the differences in costs against the differences in effectiveness. The cost effectiveness acceptability curves shows the probability of interventions being more efficient than routine care for different levels of willingness to pay per unit decrease per additional quality-adjusted life year (Fenwick et al., 2004, Westendorp et al., 2018). The cost effectiveness acceptability curves are derived from the joint density of incremental costs and incremental effects and represents the proportion of the density where the intervention is cost-effective for a range of values of willingness to pay. We estimated cost effectiveness acceptability curves via the distribution from the 5,000 bootstrapped replications. The cost effectiveness acceptability curve is determined as the proportion of the incremental cost-effectiveness ratio points where the intervention is cost-effective (Fenwick et al., 2004, Lothgren and Zethraeus, 2000, van Hout et al., 1994).

To explore whether the intervention program is more likely to be cost-effective for patients with varying pathological subtypes and hospital level, we computed separate incremental cost-effectiveness ratio and acceptability curves with varying pathological subtypes and hospital levels.

2.5. Sensitivity Analysis

We investigated the influence of imputing missing survey data on the results by reporting the incremental cost-effectiveness ratio for the observed data only (available non-missing data analysis). ~~Only observed data without missing values were included~~. To investigate the potential influence of the propensity score matching techniques on the results, we replaced one-to-one matching by Mahalanobis distance matching. In this analysis, all cases were included and Mahalanobis distance matching was performed in each of the 5,000 bootstrapped samples before estimating the incremental cost-effectiveness ratio.

We conducted all analyses in Stata version 15 for Windows (Stata Corp, College Station, TX, USA).

3. Results

3.1. Baseline characteristics in both original and matched cohorts

Table 1 summarizes patient clinical characteristics and baseline demographics. In the original cohort (before propensity score matches were performed), there were significant differences between the routine care group and the intervention group in sex, education, smoking, bedtime, number of Charlson comorbidities, levels of hospital and province. Experience with ICU, urethral invasive operation and tracheotomy within one month were significantly higher in the intervention group compared to the routine care group. There were no significant differences in age, insurance, experience of surgery and respiratory invasive operation within one month between the two groups. The average direct medical costs per patient in the routine care group was CN¥50,996, and the quality-adjusted life year was 0.175. The average direct medical costs per patient in the intervention group was CN¥48,641, and the quality-adjusted life year was 0.178.

In the matched data, the 1:1 propensity score matching yielded matched pairs of 2,966 patients in the routine care group and 2,966 patients in the intervention group, with no significant differences in sociodemographic or clinical characteristics between two groups. The average direct medical costs per patient in the routine care group was CN¥51,244, and the quality-adjusted life year in 3 months was 0.172. The average direct medical costs per patient in the intervention group was CN¥46,740, and the quality-adjusted life year in 3 months was 0.182.

3.2. Total costs, quality-adjusted life year gained, and incremental cost-effectiveness ratio of intervention group compared with routine care group in the matched cohorts

As shown in Table 2, based on the matched cohorts with imputed data, the average direct medical costs per patient in the routine care group was CN¥51,610, while it was

CN¥46,921 in the intervention group, and the health-related quality of life in 3 months for patients in the routine care group was 0.170 while it was 0.179 in the intervention group. After the program implementation, the total costs decreased CN¥4,689 (95% confidence interval [CI]: [-7815, -1562]), and the quality-adjusted life year in 3 months increased 0.010 (95% CI: [0.005, 0.014]), which resulted in an incremental cost-effectiveness ratio of CN¥ -480,077 per quality-adjusted life year (95% CI: [-1065860, -141378). ~~However,~~ After adjusting for baseline covariates using the mixed effects model, the total costs decreased CN¥4,600 (95% CI: [-7050, -2151]), and the quality-adjusted life year in 3 months increased 0.009 (95% CI: [0.005, 0.013]), with the incremental cost-effectiveness ratio decreasing significantly to CN¥-517,011 per quality-adjusted life year.

3.3. Uncertainty analysis

In Figure 1, the cost-effectiveness plane and the cost-acceptability curve are shown based on 5,000 bootstrapped replications. As can be seen, 99.6% of incremental cost-effectiveness ratios fell into the south-east quadrant, indicating that the intervention program generated greater quality-adjusted life years and was less expensive compared to routine care. At an incremental cost-effectiveness ratio of CN¥53,980 (GDP per capita for China in 2016) per quality-adjusted life year, there is a 99.8% probability that the intervention program is cost-effective, and at an incremental cost-effectiveness ratio of CN¥ 85,926 per quality-adjusted life year, there is 100% probability that the intervention program was cost-effective.

Table 3 displays subgroup analysis according to pathological subtypes and hospital levels. For ischemic stroke patients, total costs decreased CN¥5,402 (41,105 to 35,516, 95% CI:[-8508,-2296]) and quality-adjusted life year in 3 months increased 0.011 (0.167 to 0.179, 95% CI:[0.006, 0.016]), which resulted in an incremental cost-effectiveness ratio of CN¥-534,488 per quality-adjusted life year (95% CI:[-1102479, -210430]). In hemorrhagic stroke patients, total costs decreased CN¥3,328 (72,274 to 69,717, 95% CI:[-7068, 412]), and the quality-adjusted life year in 3 months increased 0.008 (0.176 to 0.181, 95% CI:[0.001, 0.015]), which resulted in an incremental cost-effectiveness ratio of CN¥-944,350 per quality-adjusted life year (95% CI:[-3922489, 88597]). In tertiary hospitals, the total costs decreased CN¥9,690 (67,430 to 60,605, 95% CI:[-13259, -6120]) and the quality-adjusted life year in 3 months increased 0.008 (0.171 to 0.180, 95% CI:[0.003, 0.013]), which resulted in an incremental cost-effectiveness ratio of CN¥ -1,377,239 per quality-adjusted life year in 3 months (95% CI:[-2987794, -648137]). Total costs increased CN¥31 in non-tertiary hospitals, but decreased CN¥1,446 (16,270 to 16,301, 95% CI:[-4396,1463]) after adjusting for baseline covariates using the mixed effects model, with the quality-adjusted life year in 3 months increasing 0.015 (0.167 to 0.178, 95% CI:[0.008,0.022]), which resulted in an incremental cost-effectiveness ratio of CN¥-101,729 per quality-adjusted life year (95% CI:[-346392, 107194]).

After bootstrapping based on the imputed data, the incremental cost-effectiveness ratios were again plotted on a cost-effectiveness plane and a cost-acceptability curve plotted in Figure 2. For hemorrhagic stroke patients, 71.14% of the ratios fell into the south-east quadrant and 17.49% fell into the north-east quadrant. At a threshold of

CN¥ 53,980 per quality-adjusted life year, there is 81.1% probability that the intervention program was cost-effective. At an incremental cost-effectiveness ratio of CN¥ 161,940 (3 times the GDP per capita for China in 2016) per quality-adjusted life year, the probability that the intervention program was more cost effective than routine care was about 84%. For ischemic stroke patients, 100% of the incremental cost-effectiveness ratios fell into the south-east quadrant, indicating that the intervention program generated greater utilities and was less expensive than routine care. In tertiary hospitals, 99.96% of the ratios fell into the south-east quadrant, indicating that the intervention program generated greater utilities and was less expensive compared to routine care. In non-tertiary hospitals, 50.12% of the incremental cost-effectiveness ratios fell into the north-east and 49.28% fell in the south-east quadrant. At a threshold of CN¥ 53,980 per quality-adjusted life year, there was a 68.7% probability that the intervention program was cost-effective. At an incremental cost-effectiveness ratio of CN¥ 161,940 per quality-adjusted life year, the intervention program had a probability of 89.6% of being optimal against routine care.

3.4 *Sensitivity analysis*

Table 4 depicts the influence of imputing missing data on the results by reporting the incremental cost-effectiveness ratio for the observed data only (available non-missing data analysis). In this analysis, only observed data without missing values were included, and we found consistent results across these two data sets. Employing the Mahalanobis distance matching in Table 4, we also investigated the potential influence of the propensity score matching techniques on the results by reporting the incremental cost-effectiveness ratio (ICER). We found consistent results by these two matching techniques.

4. Discussion

Researchers from different countries recommend that stroke care can tackle the stroke cost burden (Grieve et al., 2000, The, 2019, van Exel et al., 2005). We developed the standardized nursing intervention program based on evidence-based nursing practice. Nurses were trained in the intervention program, then the intervention program was applied to immobile stroke patients, which showed that integrated nursing care could significantly lower immobile stroke patient costs and improve the health care of stroke patients. After adjusted for baseline covariates using the mixed effects model, the result indicates that a nurse-led intervention program for immobile stroke patients decreased stroke care costs by CN¥4,600 after adjustment for baseline covariates and increased the quality-adjusted life year in 3 months at 0.009. The intervention program led to a significant improvement in general health status for immobile stroke patients in an unequivocally cost-efficient way, which improved the health-related quality of life at an expected cost saving to health care system of CN¥517,011. A previously study showed that compared to routine nursing care, an intervention program can decrease the incidences of major immobility complications and improved clinical outcomes for immobile patients (Liu et al., 2019). While achieving improved health outcomes, this paper shows that implementing a nurse-led intervention program can also save costs.

To our knowledge, this is the largest multicenter study of a nursing program for immobile stroke patients and the first report on the economic evaluation of an intervention program conducted in China. After the application of the intervention program, the quality-adjusted life year improved +0.01 in 3 months, which is similar to the results of an American nurse-led disease management program for heart failure (Hebert et al., 2008).Research from the Netherlands indicated that the incremental cost-effectiveness ratio of their integrated stroke services in Delft was €19,350 less per quality-adjusted life year gained (van Exel et al., 2005), and a stroke care model from Copenhagen suggested that the incremental cost-effectiveness ratio was US$21,579 per quality-adjusted life year gained for continent patients and US$37,444 for incontinent patients (Grieve et al., 2000). The incremental cost-effectiveness ratios from these studies were much higher than the incremental cost-effectiveness ratio of our China intervention program. Part of the reason is that the Dutch and Swedish stroke care models were more structured than our intervention program. Our program contains major immobility complications standardized nursing care interventions and skills required by nurses working in hospital stroke facilities, while the integrated stroke services in the Netherlands contained one hospital stroke unit, one nursing home stroke unit, one rehabilitation center and one home care provider, all supported by a stroke nurse (van Exel et al., 2005), thus the resources and costs included in their model may lead to incremental cost-effectiveness ratios somewhat higher than the incremental cost-effectiveness ratios for our program. Although the stroke care models in different countries may vary between countries, generally, these integrated stroke nursing measures were cost-efficient. Therefore, our results confirm evidence that, compared with routine stroke nursing care, improved standardized nursing interventions can save costs and are also more effective in health-related quality of life outcomes than routine care.

In ischemic stroke patients, 100% of the ratios fall into the south-east (less cost and high quality-adjusted life years) quadrant, indicating that the intervention program saved costs while achieving health outcome benefits for patients. While in hemorrhagic stroke patients, at a threshold of CN¥ 53,980 per quality-adjusted life year, there was an 81.1% probability that the intervention was cost-effective，and at an incremental cost-effectiveness ratio of CN¥ 161,940 (3 times the GDP per capita for China in 2016) per quality-adjusted life year, there was an 84.0% probability that the intervention was cost-effective. Although the health-related quality of life improved significantly in both ischemic and hemorrhagic stroke patients, the cost did not decrease significantly in patients with hemorrhagic stroke, but did decrease significantly for ischemic stroke patients. Compare with hemorrhagic stroke patients, deep vein thrombosis and pneumonia are frequent complications in ischemic stroke, which significantly contribute to hospital cost (Ali et al., 2009, Dennis et al., 2016, Kong et al., 2016). Through implementing the intervention program, ischemic stroke patients may reduce hospital costs due to pneumonia and deep vein thrombosis, but not for hemorrhagic stroke patients that had a much lower incidence of pneumonia and deep vein thrombosis.

In tertiary hospitals, 99.96% of the ratios fall into the south-east (less cost and high quality-adjusted life years) quadrant, indicating that the intervention program generates greater utilities and is less expensive compared to routine care. In non-tertiary hospitals, there was a 68.7% probability that the intervention is cost-effective at a threshold of

CN¥ 53,980 per quality-adjusted life year. The quality-adjusted life year improved in non-tertiary hospitals was much more than the tertiary hospitals (0.015 versus 0.008), while there was no significant reduction in total costs in non-tertiary hospitals compare with the tertiary hospitals (-1466 versus -9690). The potential reasons for this difference may be the disparities in major immobility complications related nursing care (Xiaojing et al., 2016). Before the intervention program implementation, nursing care were less standardization in non-tertiary hospitals compared to tertiary hospitals. The intervention program training will significantly improve standards of care in non-tertiary hospitals, but increase the costs related to nursing care, offsetting the reduction of the costs due to major immobility complications, which may explain the insignificant improvement in total cost. Further, the intervention program's large improvement in nursing care will lead to large improvements in non-tertiary hospitals' quality-adjusted life year.

Our study has several potential limitations. First, we conducted a historical and comparative study and the routine care group and intervention group were not conducted at the same time, so there may be potential bias due to changes in the treatment trends during the study periods. Mediating this concern is that the gap between these periods was only 1 year. Also the quality control system was applied to the patients in each hospital (Liu et al., 2019), with a structured, systematic nursing intervention model implemented for each patient， so the patients in this study experienced homogeneous care. Second, we only had a limited 3 month follow up, which means future research should conduct a long-term follow-up study of the health-related quality of life. Third, we did not calculate the indirect and intangible costs of the intervention program, which means that the effectiveness of this program was probably underestimated.

A strong point of our study is that the analysis was based on individual patient data collected at 25 hospitals across China. This is the first study to compare the costs and effects of implementing an intervention program on immobile stroke patients, providing a realistic picture of the health benefits that could be achieved if the program were implemented on a nationwide scale. Previous studies on the cost effectiveness of nurse-led disease or illness complications management programs were conducted in single hospital (Avşar and Karadağ, 2018, Gallefoss, 2004), thus lacking generalizability. We applied propensity score matching to reduce any potential biases between the two groups. We found that there was no significant difference between the two groups after matching, which indicates the propensity score matching improved the reliability of our results. We also replaced missing values data with 10 imputed values, using multiple imputation by chained equations. Finally, the sensitivity analyses suggest that the results are robust across different matching techniques and data sets.

Our results provide useful information for decision makers who draft policy for health insurance services. One recommendation is for insurance policies to re-customize the proportion of reimbursement for immobile stroke patients for different pathological subtypes and levels of hospitals. We also recommend developing clinical nursing practice care bundles for subtypes of strokes as well as other illnesses (Lavallée et al., 2017, Wunderink and Waterer, 2017) , which will improve patients' health-related quality of life, attenuate the incidence of major immobility complications and save hospital costs. Policymakers should construct support networks for non-tertiary hospitals to help them improve their knowledge, attitudes and standards of nursing care. In addition, with population aging and an ongoing high prevalence of risk factors, such as hypertension, obesity and diabetes, in the population, the development and implementation of similar nursing care intervention programs should be a priority in the "Healthy China 2030" Planning Outline. Finally, China should promote integrated stroke services, which include hospital stroke units, nursing home stroke units, rehabilitation centers, home-visit nursing utilization and home-visit nurses (Grieve et al., 2000).

5. Conclusions

At less than CN¥-517,011 per quality-adjusted life year saved, our nurse-led intervention program was cost-effective over 3 months, especially for ischemic stroke patients and tertiary hospitals. In terms of cost-effectiveness, this program was particularly promising for immobile patients with stroke who receive nursing care in a hospital setting. Our findings suggest improved health outcomes for the intervention group patients and cost-effectiveness for hospitals. The wider adoption of such nursing interventions programs may be a sensible approach to reducing the burden of stroke in non-tertiary hospitals and for immobile patients suffering non-stroke illnesses.

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Conflict of interest

We declare no competing interests relevant to this manuscript.

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Authors' contributions

XW conceived and designed this study and reviewed the manuscript, HL prepared and edited the manuscript. DZ performed statistical analyses and drafted the tables. BS, JJ, YL, XW, SC, and SN recruited participants, collected data, and edited the manuscript.

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Table 1. Baseline characteristics at the intervention program initiation in the original and the matched cohort.

	Original data			Matched data		
	Routine Care Group (n=3891)	Intervention Group (n=3762)	*P*-value	Routine Care Group (n=2966)	Intervention Group (n=2966)	*P*-value
Variables Used for Matching						
Age group, n (%)			0.199			0.887
0-59 years old	1410(36.2)	1292(34.3)		1036(34.9)	1049(35.4)	
60-74 years old	1460(37.5)	1437(38.2)		1138(38.4)	1120(37.8)	
75 years old and above	1021(26.2)	1033(27.5)		792(26.7)	797(26.9)	
Female, n (%)	1659(42.6)	1507(40.1)	0.022	1227(41.4)	1258(42.4)	0.415
Education, n (%)			<0.001			0.586
None	809(20.8)	588(15.6)		508(17.1)	545(18.4)	
Primary school	1218(31.3)	1390(36.9)		1026(34.6)	995(33.5)	
Junior high school	996(25.6)	988(26.3)		765(25.8)	772(26.0)	
High school and above	868(22.3)	796(21.2)		667(22.5)	654(22.0)	
Smoking, n (%)			<0.001			0.578
Never smoke	2708(69.6)	2618(69.6)		2069(69.8)	2079(70.1)	
Ever smoked	936(24.1)	752(20.0)		662(22.3)	673(22.7)	
Smoking now	247(6.3)	392(10.4)		235(7.9)	214(7.2)	
Insurance, n (%)			0.282			0.684
No insurance	766(19.7)	803(21.3)		619(20.9)	647(21.8)	
NCMS	1578(40.6)	1465(38.9)		1131(38.1)	1141(38.5)	
URBMI	666(17.1)	643(17.1)		532(17.9)	504(17.0)	
UEBMI	881(22.6)	851(22.6)		684(23.1)	674(22.7)	
Bedtime, n (%)			<0.001			0.329

1-3 days	1179(30.3)	945(25.1)		800(27.0)	862(29.1)	
4-6 days	695(17.9)	764(20.3)		560(18.9)	532(17.9)	
7-12 days	935(24.0)	982(26.1)		745(25.1)	735(24.8)	
13 days and above	1082(27.8)	1071(28.5)		861(29.0)	837(28.2)	
Experience of ICU, n (%)	978(25.1)	1061(28.2)	0.002	782(26.4)	771(26.0)	0.745
Experience of surgery, n (%)	813(20.9)	821(21.8)	0.321	631(21.3)	621(20.9)	0.750
Respiratory invasive operation within one month, n (%)	108(2.8)	99(2.6)	0.698	82(2.8)	85(2.9)	0.814
Tracheotomy within one month, n (%)	569(14.6)	704(18.7)	<0.001	512(17.3)	496(16.7)	0.580
Urethral invasive operation within one month, n (%)	1154(29.7)	1385(36.8)	<0.001	998(33.6)	973(32.8)	0.491
Number of Charlson comorbidities, n (%)			0.002			0.983
0-3	1217(31.3)	1068(28.4)		881(29.7)	890(30.0)	
4	789(20.3)	719(19.1)		585(19.7)	585(19.7)	
5	934(24.0)	934(24.8)		714(24.1)	718(24.2)	
6 and above	951(24.4)	1041(27.7)		786(26.5)	773(26.1)	
Tertiary hospital, n (%)	2754(70.8)	2511(66.7)	<0.001	2047(69.0)	2050(69.1)	0.933
Province, n (%)			<0.001			0.652
Beijing	177(4.5)	210(5.6)		162(5.5)	170(5.7)	
Sichuan	577(14.8)	591(15.7)		495(16.7)	491(16.6)	
Henan	271(7.0)	257(6.8)		200(6.7)	190(6.4)	
Zhejiang	1461(37.5)	1155(30.7)		957(32.3)	979(33.0)	
Hubei	935(24.0)	842(22.4)		717(24.2)	743(25.1)	
Outcomes Variables						
Total costs	50996(63755)	48641(59882)		51244(64849)	46740(57668)	
QALY (EQ-5D)	0.175(0.087)	0.178(0.085)		0.172(0.088)	0.182(0.084)	

Abbreviations, NCMS: new cooperative medical system; URBMI: urban resident basic medical insurance; UEBMI: urban employee basic medical insurance; ICU: intensive care unit; QALY: quality-adjusted life year; EQ-5D: EuroQol five-dimensional questionnaire. The Chi-square test was used for balance in the samples.

Table 2. Total costs, QALY gained and ICER of routine care group compared with intervention group in the matched cohort (Imputed data).

	Routine Care Group (n=2966)	Intervention Group (n=2966)	**Difference (95% CI)**	**Adjusted Difference (95% CI)**
Total costs	51610	46921	-4689(-7815, -1562)	-4600 (-7050, -2151)
QALY (EQ-5D)	0.170	0.179	0.010(0.005, 0.014)	0.009(0.005, 0.013)
ICER (RMB per QALY gained)	-	-	-480077(-1065860, -141378)	-517011(-1111442, -203912)

Abbreviations, CI: confidence interval; QALY: quality-adjusted life year; EQ-5D: EuroQol five-dimensional questionnaire; ICER: incremental cost-effectiveness ratio. Adjusted difference is from the mixed effects model. 95% CIs for ICERs were bootstrapped.

Figure 1 Five thousand bootstrapped replicates of incremental costs and incremental quality-adjusted life years for intervention group versus routine care group and the resulting cost-effectiveness acceptability curve.

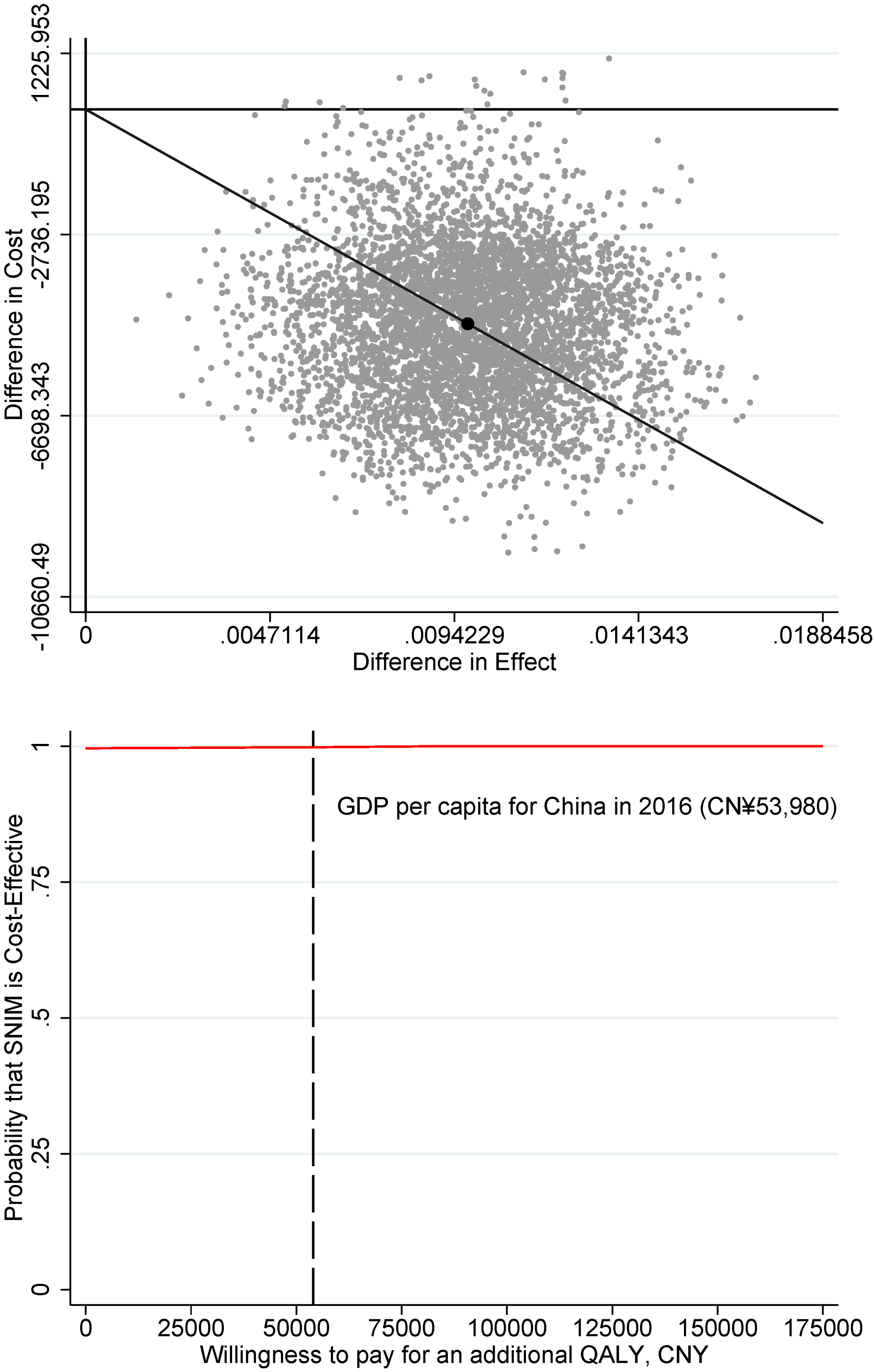


Table 3. Subgroup analysis of the effects of the intervention program on the ICER (Imputed data).

		Routine Care Group	Intervention Group	**Difference (95% CI)**	**Adjusted Difference (95% CI)**
Pathological subtypes					
Ischemic	Total costs	41105	35516	-5589(-9107,-2071)	-5402(-8508,-2296)
	QALY (EQ-5D)	0.167	0.179	0.012(0.007, 0.018)	0.011(0.006, 0.016)
	ICER (RMB per QALY gained)	-	-	-459339(-928598, -190814)	-534488(-1102479, -210430)
Hemorrhagic	Total costs	72274	69717	-2557(-8747, 3633)	-3328(-7068, 412)
	QALY (EQ-5D)	0.176	0.181	0.005(-0.003, 0.013)	0.008(0.001, 0.015)
	ICER (RMB per QALY gained)	-	-	-513366(-13069294, 11180594)	-944350(-3922489, 88597)
Hospital levels					
Tertiary hospitals	Total costs	67430	60605	-6825(-10951, -2698)	-9690(-13259, -6120)
	QALY (EQ-5D)	0.171	0.180	0.009(0.003, 0.014)	0.008(0.003, 0.013)
	ICER (RMB per QALY gained)	-	-	-761236(-1940061, -293216)	-1377239(-2987794, -648137)
Non-Tertiary hospitals	Total costs	16270	16301	31(-2085, 2146)	-1466(-4396,1463)
	QALY (EQ-5D)	0.167	0.178	0.011(0.003, 0.019)	0.015(0.008,0.022)
	ICER (RMB per QALY gained)	-	-	2722(-212001, 383822)	-101729(-346392, 107194)

Abbreviations, CI: confidence interval; QALY: quality-adjusted life year; EQ-5D: EuroQol five-dimensional questionnaire; ICER: incremental cost-effectiveness ratio. Adjusted difference is from the mixed effects model. 95% CIs for ICERs were bootstrapped.

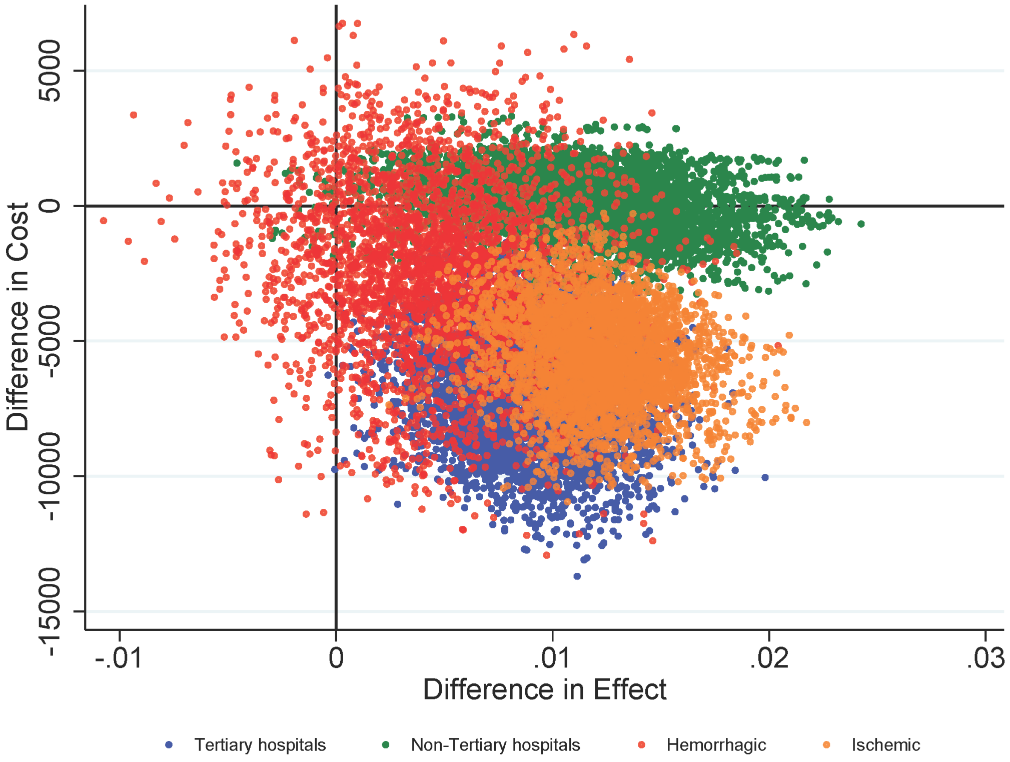
Table 4. Sensitivity analysis for impute and propensity score matching techniques

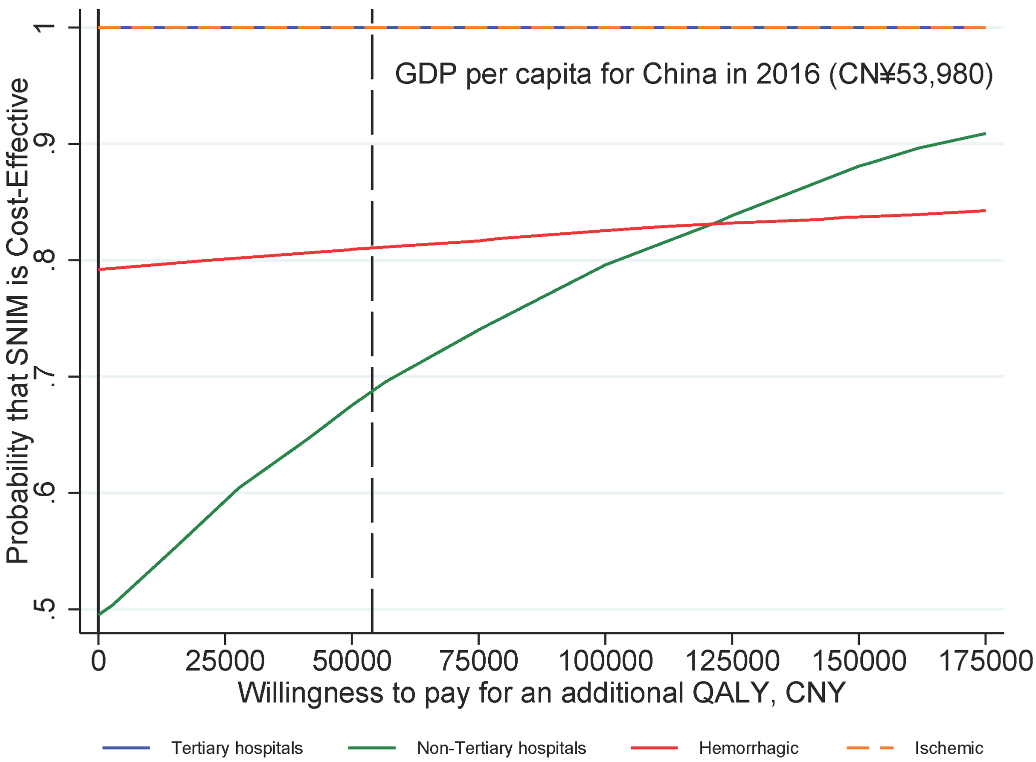
		Routine Care Group	Intervention Group	**Difference (95% CI)**	**Adjusted Difference (95% CI)**
Complete cases(n=5039) [a]	Total costs	51263	46729	-4535(-7638.294, -1431.036)	-4557(-6696,-2418)
	QALY (EQ-5D)	0.172	0.182	0.009(0.005, 0.014)	0.009(0.005,0.013)
	ICER (RMB per QALY gained)	-	-	-482437 (-1011852, -156980)	-491635(-952623,-228385)
Mahalanobis distance matching	Total costs	50186	48547	-1639(-5692, 2414)	-1885(-3792,-139)
	QALY (EQ-5D)	0.171	0.179	0.008(0.002, 0.015)	0.007(0.002,0.013)
	ICER (RMB per QALY gained)	-	-	-197790 (-1241662,411912)	-257905(-1190745,-9907)

[a] Original data without imputing missing values for the dependent variable (s). Adjusted difference is from the mixed effects model. 95% CIs for ICERs were bootstrapped.

Abbreviations, CI: confidence interval; QALY: quality-adjusted life year; EQ-5D: EuroQol five-dimensional questionnaire; ICER: incremental cost-effectiveness ratio.

Figure 2 Subgroup analysis according to pathological subtypes and hospital levels.





Supplemental On-line Information

Details of the intervention program

Between November 2015 and June 2016, we collected the baseline data in cooperative hospitals, such as the frequency of complications in immobile stroke patients, nursing interventions being implemented for stroke and complications. Therefore, we found that the incidence of four major immobility complications was high (pressure injuries, pneumonia, deep vein thrombosis, urinary tract infections). Meanwhile, an evidence-based searching team consisting of nine master's degree nurses, searched for relevant published papers based on PubMed, ScienceDirect, Embase, etc. with immobile, complications, stroke, pneumonia, pressure injuries, urinary tract infections, etc. as modifiers, then used the Joanna Briggs Institute critical appraisal tools to evaluate the quality of these papers, and extracted effective nursing interventions. In June 2016, based on baseline data and evidence-based search report, 11 expert consultation meetings consisting of 162 nursing specialists with clinical and management background from 6 provinces in China were held. We then constructed the intervention program based on the baseline data, evidence-based results, and expert opinions.

Characteristics of the intervention program

As shown in Supplementary Table 1, there are six elements in the intervention program, including risk factors assessment, observation, nursing precaution, nursing intervention and nursing operation according to complications and health education related to complications. Each element in our program contained critical points, reflecting the knowledge and skills required by nurses to provide standardized nursing care delivery.

Training, data collection and quality control

From August through September in 2016, we trained nurses using our intervention program through on-site centralized teaching and online learning, the trainer were the member of the core research team, who are registered nurse with master's degree, with at least 5 years of clinical working experience and passed the clinical nursing operation exam organized by Peking Union Medical College Hospital, which means the knowledge and clinical nursing operation skills are credible. A total of 12 batches of on-site lectures were organized, and the specific content of the program were taught and tested in the class. We also uploaded the recorded videos of the theoretical lectures that recorded in the class and the nursing operations to an online self-learning platform, in order to help nurses to recall the related knowledge and skills. Between September and October 2016, we pre-tested the program on immobile patients in the 25 hospitals across all six major regions of China to ensure nurses could apply correctly interventions on patients. Finally, we implemented this program formally and collected data between November 2016 and July 2017.

Our study appointed a coordinator who was in charge of internal logistics in each cooperating hospital, and at least two registered head nurses in each ward were designated to oversee patient data collection using a case report form (CRF). To ensure accurate data collection, each nurse received systematic training on completing the CRF before they recorded patients' information daily on the web-based online CRF. From the day of enrolment, all patients were observed and recorded for 90 days, unless there was death in hospital or treatment was abandoned.

Supplementary Table 1 Key points of the intervention program.

Elements	Pressure injuries (PIs)	Deep vein thrombosis (DVT)	Pneumonia	Urinary tract infections (UTIs)
Risk assessment	Identify risk factors by Braden Scale and NRS-2002, pressure area assessment	Identify risk factors by Caprini Risk Assessment Scale	Assess vital signs and risk factors, including swallowing disorders, medical treatments, environmental factors, etc.	Assess gender, age, function and structure of urinary system, iatrogenic factors, immunity factors, metabolic factors and lifestyle behaviors
Observation	Skin surveillance	Limb observation (edema, pain, tenderness, fever, etc.)	Observe lung symptoms and vital signs, etc.	Observe symptoms associated with voiding and vital signs
Precaution	Frequent position changes, use of devices (e.g. apply decompression tool, alternating pressure mattresses, use of padded heel boots)	Daily measurement of calf circumference, mechanical interventions (e.g. plantar arteriovenous pump), drug prevention, etc.	Oral care, prevention of VAP, etc.	Perineal care, possibilities to go to the toilet or sitting upright when urinating
Nursing intervention	Application of pressure reduction dressings, use of devices, change position, etc.	Mechanical interventions, medication care, etc.	Medication care, oral care, mechanical ventilation care, etc.	Medication care, perineal care, catheter maintenance, etc.
Nursing operation	Position changes and replace pressure reduction dressings	Wear off antithrombotic stockings, ankle pump exercise	Respiratory exercises, suctioning, inhalation, postural drainage, etc.	Catheterization, catheter maintenance, hand hygiene, etc.
Health education	Prevention of pressure injuries and home care measures after the occurrence of pressure injuries	Methods of ankle pump exercise and wear antithrombotic stockings, knowledge of using anticoagulant drugs	Knowledge of preventing pneumonia, exercise training of respiratory function, methods of oral feeding, knowledge of using antibiotics	Drink water according to physical condition, do physical activities, methods of perineal care, knowledge of using antibiotics, hand hygiene

Supplementary Table 2 Characteristics between samples with and without missing data

	Without missing data	With missing data	*P -value*
Age group, n (%)			0.192
0-59 years old	2291(35.3)	411(35.3)	
60-74 years old	2479(38.2)	418(35.9)	
75 years old and above	1719(26.5)	335(28.8)	
Female, n (%)	2703(41.7)	463(39.8)	0.231
Education, n (%)			< 0.001
None	1214(18.7)	183(15.7)	
Primary school	2266(34.9)	342(29.4)	
Junior high school	1648(25.4)	336(28.9)	
High school and above	1361(21.0)	303(26.0)	
Smoking, n (%)			0.254
Never smoke	4518(69.6)	808(69.4)	
Ever smoked	1417(21.8)	271(23.3)	
Smoking now	554(8.5)	85(7.3)	
Insurance, n (%)			< 0.001
No insurance	1380(21.3)	189(16.2)	
NCMS	2581(39.8)	462(39.7)	
URBMI	1112(17.1)	197(16.9)	
UEBMI	1416(21.8)	316(27.1)	

Bedtime, n (%)			< 0.001
1-3 days	1878(28.9)	246(21.1)	
4-6 days	1241(19.1)	218(18.7)	
7-12 days	1644(25.3)	273(23.5)	
13 days and above	1726(26.6)	427(36.7)	
Experience of ICU, n (%)	1518(23.4)	521(44.8)	< 0.001
Experience of surgery, n (%)	1378(21.2)	256(22.0)	0.562
Respiratory invasive operation within one month, n (%)	151(2.3)	56(4.8)	< 0.001
Tracheotomy within one month, n (%)	998(15.4)	275(23.6)	< 0.001
Urethral invasive operation within one month, n (%)	2008(30.9)	531(45.6)	< 0.001
Number of Charlson comorbidities, n (%)			
0-3	1931(29.8)	354(30.4)	0.399
4	1277(19.7)	231(19.8)	
5	1606(24.7)	262(22.5)	
6 and above	1675(25.8)	317(27.2)	
Tertiary hospital, n (%)	4338(66.9)	927(79.6)	< 0.001
Province, n (%)			< 0.001
Beijing	327(5.0)	60(5.2)	
Sichuan	1007(15.5)	161(13.8)	
Henan	318(4.9)	210(18.0)	
Zhejiang	2321(35.8)	295(25.3)	
Hubei	1644(25.3)	133(11.4)	

Abbreviations, NCMS: new cooperative medical system; URBMI: urban resident basic medical insurance; UEBMI: urban employee basic medical insurance; ICU: intensive care unit.