Rates of intravenous thrombolysis and endovascular therapy for acute ischaemic stroke in China between 2019 and 2020

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Summary

Background In recent years, a series of initiatives have been launched to promote intravenous thrombolysis (IVT) and endovascular therapy (EVT) for acute ischaemic stroke (AIS) in China. We aimed to update the rates of IVT and EVT in China between 2019 and 2020 and to evaluate the current IVT and EVT according to hospital grades.

Methods Cross-sectional data on patients receiving IVT/EVT were derived from the Bigdata Observatory platform for Stroke of China (BOSC). The monthly number of discharged patients with a principal diagnosis of AIS was derived from the first pages of medical records of each hospital. The rates and information of IVT and EVT were analysed according to hospital grades.

Findings During this period, 938 tertiary hospitals and 786 secondary hospitals from 31 provinces continuously reported data to the BOSC. The overall IVT rate for AIS was 5.64%, and the EVT rate was 1.45%. The IVT rate in secondary hospitals was higher than that in tertiary hospitals (6.39% vs. 5.39%, P < 0.001), whereas the EVT rate in secondary hospitals was much lower than that in tertiary hospitals (0.29% vs. 1.84%, P < 0.001). Significant differences in demographic and clinical characteristics of patients receiving IVT/EVT were also shown between tertiary and secondary hospitals.

Interpretation The rates of IVT and EVT for AIS have greatly increased in China, but there is still a large gap compared with developed countries. Hospital inhomogeneity in IVT and EVT suggests the importance of developing a region-specific network for stroke treatment.

Abbreviations: IVT, Intravenous thrombolysis; EVT, Endovascular therapy; AIS, Acute ischaemic stroke; BOSC, Bigdata Observatory platform for Stroke of China
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Keywords: Intravenous thrombolysis rate; Endovascular therapy rate; Acute ischaemic stroke; Tertiary hospitals; Secondary hospitals; Bigdata Observatory platform for Stroke of China

Research in context

Evidence before this study

In China, less than 3% of patients with acute ischaemic stroke received intravenous thrombolysis before 2013 and only 0.45% of patients received endovascular therapy in tertiary hospitals in 2015, although both intravenous thrombolysis and endovascular therapy are strongly recommended by Chinese guidelines for acute ischaemic stroke. We searched PubMed, ScienceDirect, and Google Scholar on August 30, 2021, for studies published in English describing the rates of intravenous thrombolysis and endovascular therapy for acute ischaemic stroke in China, using the search terms (1) “intravenous thrombolysis” or “ alteplase” or “ recombinant tissue plasminogen activator” and “ ischaemic stroke” and “ China” and (2) “endovascular therapy” or “ embolectomy” or “ thrombectomy” and “ ischaemic stroke” and “ China”. We also searched Wanfang Data using the same terms in Chinese. We identified ten articles that analysed the rate of intravenous thrombolysis in China. Only five national-level studies covered large samples of patients with acute ischaemic stroke and explicitly showed the rate of intravenous thrombolysis. We identified two articles that analysed the rate of endovascular therapy in China. Only one national-level study explicitly showed the rate of endovascular therapy. Considering the years of effort to promote intravenous thrombolysis and endovascular therapy, it is urgent to update the situation of intravenous thrombolysis and endovascular therapy in China.

Added value of this study

We found that the rates of intravenous thrombolysis and endovascular therapy have greatly increased in China, but there is still a large gap compared with developed countries. We also showed inhomogeneity in intravenous thrombolysis and endovascular therapy between tertiary and secondary hospitals in China. To the best of our knowledge, we are the first to compare intravenous thrombolysis and endovascular therapy in detail between tertiary and secondary hospitals in China.

Implications of all the available evidence

The development of intravenous thrombolysis and endovascular therapy emphasizes the need to implement training and accreditation of acute stroke management and to develop a region-specific network for stroke treatment in China. The hospital inhomogeneity in intravenous thrombolysis and endovascular therapy suggests that an improvement in the division of labor for stroke treatment between secondary and tertiary hospitals should be taken into consideration.

Introduction

China bears the heaviest stroke burden in the world. With the continuous promotion of stroke care and prevention, the mortality rates of stroke patients have declined gradually, but the incidence of stroke is still increasing as a result of ageing of the Chinese population. Stroke has become the leading cause of death and disability in China, accounting for 1.57 million deaths in 2018. Early reperfusion therapy, including intravenous thrombolysis (IVT) and endovascular therapy (EVT), is the most effective evidence-based treatment for acute ischaemic stroke (AIS). Despite strong recommendations from guidelines, however, previous studies reported that only 10% to 20% of patients with AIS arrived at hospitals within three hours, and less than 3% of patients received IVT before 2013 in China. Only 0.45% of patients received EVT in tertiary hospitals in 2015. These rates are much lower than those in developed countries.

The China Stroke Prevention Project Committee (CSPPC) was established in 2011 by the Ministry of Health of China and is responsible for the quality improvement of stroke prevention and treatment. With the goals of setting standards, improving quality, and minimizing variation in China, the CSPPC initiated certification processes for stroke centres in 2015. Through the rigorous precertification process (stroke centre application, CSPPC committee review, and onsite evaluation) and postcertification process (periodical teaching program and monitoring), the CSPPC aims to improve the quality of stroke management, including the rates of IVT and EVT. With the increased number of certified stroke centres, CSPPC has been releasing stroke emergency maps since 2016 to guide stroke patients and ambulances to reach regional stroke centres in a timely manner. Notably, the construction of stroke...
centres began in tertiary hospitals and gradually extended to secondary hospitals. Similarly, IVT and EVT were also promoted earlier in tertiary hospitals than in secondary hospitals. Due to the significant differences in technical level and medical equipment across different grades of hospitals in China, the inhomogeneity of stroke care has been shown between tertiary and secondary hospitals.\textsuperscript{9} However, IVT and EVT have rarely been compared across different grades of hospitals.

After years of effort, it is crucial to investigate the current situation regarding IVT and EVT rates nationwide, as they are the pivotal steps in AIS care. Dynamic updates on the stroke care situation at the national level would inform national health care plans and implementation, be helpful for effective prevention and intervention, and eventually contribute to achieving the goal of Healthy China 2030.\textsuperscript{10} Therefore, the objective of the present analysis was to update the rates of IVT and EVT in China between 2019 and 2020 and to evaluate the current IVT and EVT across different grades of hospitals.

Methods

Data source

The present cross-sectional analysis was based on the data derived from the direct report system in the Bigdata Observatory platform for Stroke of China (BOSC). Detailed information about the platform has been described in previous studies.\textsuperscript{11,12} The direct report system was established by the CSPPC to monitor and improve the quality of stroke management, especially early reperfusion therapy for AIS, in China. The CSPPC aims to cover most hospitals that are capable of providing stroke management in China. These hospitals report all patients receiving IVT, EVT, cerebral hemorrhage operation, carotid artery endarterectomy, carotid artery stenting, or cerebral aneurysm surgery monthly using the system. The data include demographic information, diagnosis, severity, treatment, and complications. Based on these data, the CSPPC accesses and ranks the quantity and quality of stroke management for each hospital on the website every month. The quantity and quality of stroke management serve as qualifications for stroke centres. The monthly number of discharged patients with a principal diagnosis of AIS was derived from the first pages of medical records of each hospital. The present analysis was approved by the medical ethics committee of Brain Hospital of Hunan Province (Z2017006). Approval was received from the medical ethics committee to report the data on the BOSC without requiring individual informed consent.

The BOSC platform, training, and quality control

Reporting stroke data on this platform is an obligatory requirement for all qualified stroke centres for the purpose of monitoring stroke care quality. The quality of the data acquisition and reporting is maintained with uniform trainings and implementing standardized protocols. A specific staff team organized by each hospital and trained by the CSPPC stroke program is responsible for data reporting, data review, and data management. A logical validation is included in the reporting system to check the completeness and plausibility of the data. Hospitals that did not continuously report data (including the patient-level data of all cases receiving IVT/EVT and the monthly number of all discharged patients with a principal diagnosis of AIS) between 2019 and 2020 were excluded.

Definitions

The diagnosis of AIS was made according to the International Classification of Diseases, 10th version (ICD-10) code I63. We included subjects for analysis as follows: (1) age $\geq$ 18 years old; (2) admission within 14 days after symptom onset; and (3) hospitalization between January 1, 2019, and December 31, 2020. Complications after IVT/EVT were assessed by trained neurologists in each hospital mainly according to imaging features within seven days after receiving IVT/EVT. Intracranial hemorrhage was defined as intracranial bleeding on computed tomography. Arterial dissection was diagnosed with a localized contrast pocket, an intimal flap, or a double lumen on digital subtraction angiography (DSA) images or computed tomography angiography (CTA) images. Reocclusion was defined using DSA or CTA. All hospitals were tertiary hospitals and secondary hospitals accredited by national health authorities according to hospital scale, service, technical level, and medical equipment. In China, secondary hospitals are responsible for providing comprehensive health services for a region. Tertiary hospitals are comprehensive, referral, general hospitals at the city, provincial or national level, and they are responsible for providing specialist health services and play a larger role with regard to medical education and scientific research.

Statistical analyses

The rate of IVT/EVT was defined as the number of AIS patients receiving IVT/EVT divided by the number of all discharged patients with a principal diagnosis of AIS. The rates of IVT and EVT and the characteristics of patients receiving IVT/EVT were analysed according to different grades of hospitals. The Kolmogorov–Smirnov test was used to assess the data normality of continuous variables. Nonnormally distributed data are presented as medians (1st–3rd quartiles), and categorical variables are presented as numbers and percentages. First, we compared the characteristics of patients between tertiary and secondary hospitals. Mann–Whitney tests and chi-
squared tests were performed for continuous variables and categorical variables, respectively. Original statistical significance was set at \( P < 0.05 \). A Bonferroni correction for multiple comparisons was conducted in these analyses, and the corrected statistical significance was set at \( P < 0.05/n \) (\( n \) indicates the total number of comparisons being performed), i.e., \( P < 0.003 \) (0.05/18 tests) for IVT therapy and \( P < 0.003 \) (0.05/16 tests) for EVT therapy. Next, general linear models or logistic models were constructed to determine whether the differences in characteristics related to IVT/EVT were still significant between tertiary and secondary hospitals after adjusting for age, sex, ethnicity, patient source, ambulance to hospitals, and hospital regions. Binary logistic regression model was adopted for binary dependent variables, and multinomial logistic regression model was adopted for categorical dependent variables with more than two categories. Logistic models for the complication of IVT/EVT were further adjusted for age, sex, ethnicity, patient source, ambulance to hospitals, and hospital regions. The IVT rate in China increased from 0.45% to 1.45% during 2015–2020. In contrast, the EVT rate in Germany increased from 4.7% to 7.2% during 2016–2019. There were disparities in the rates among different Chinese regions. The EVT rate in Southwest China was the highest, whereas the EVT rate in East China was the highest (eTables 1 and 2 in Supplementary Material). In addition, both the IVT and EVT rates were significantly higher in 2020 than in 2019 (5.95% vs. 3.29% and 1.57% vs. 1.33% for IVT and EVT, respectively) (eTables 3 and 4 in Supplementary Material).

**Results**

From 2019 to 2020, 1736 hospitals, including 942 tertiary hospitals and 794 secondary hospitals, from 31 provinces reported data to the BOSC. Four tertiary hospitals and eight secondary hospitals were excluded due to suspended reporting. Thus, 192247 AIS patients receiving IVT and 49551 AIS patients receiving EVT from 938 tertiary hospitals and 786 secondary hospitals were involved in the analysis. As shown in Table 1, compared with AIS patients receiving IVT in secondary hospitals, those in tertiary hospitals were more likely to be male, of Han ethnicity, sent to hospitals by ambulance, and admitted from the emergency department. The comparisons of clinical characteristics of patients receiving IVT between secondary and tertiary hospitals were adjusted for age, sex, ethnicity, patient source, ambulance to hospitals, and hospital regions. As shown in Table 3, patients in tertiary hospitals had significantly higher proportions of “minor stroke” (NIHSS ≤ 3) and short DNT (≤ 30 min) than those in secondary hospitals. However, the onset-needle-time (ONT) was significantly longer in tertiary hospitals than in secondary hospitals (\( \beta = 8.57, P < 0.001 \)). For the therapeutic options for IVT, recombinant tissue type plasminogen activator (rt-PA) was more frequently used in tertiary hospitals (OR = 2.16, 95%CI 2.11-2.21, \( P < 0.001 \)).

**IVT and EVT rates**

From 2019 to 2020, 3408704 discharged patients with a principal diagnosis of AIS on the first pages of medical records were reported by the 938 tertiary hospitals and 786 secondary hospitals. Thus, the overall IVT and EVT rates between 2019 and 2020 were 5.64% and 1.45%, respectively (Figure 1). As shown in Table 3, the IVT rate in China during 2006–2013 was approximately 2%, much lower than our findings. On the other hand, the IVT rate in North American and European countries has greatly increased from 1–4% to 10–15% during the past 20 years. As shown in Table 4, the EVT rate in China increased from 0.45% to 1.45% during 2015–2020. There were disparities in the rates among different Chinese regions. The EVT rate in Southwest China was the highest, whereas the EVT rate in East China was the highest (eTables 1 and 2 in Supplementary Material). In addition, both the IVT and EVT rates were significantly higher in 2020 than in 2019 (5.95% vs. 3.29% and 1.57% vs. 1.33% for IVT and EVT, respectively) (eTables 3 and 4 in Supplementary Material).
## Table 1: Demographic and clinical characteristics of patients receiving IVT from different grades of hospitals.

Values are presented as numbers (percentages) or medians (interquartile range). A Mann-Whitney test was applied in the analyses of numerical variables. The \( \chi^2 \) test was applied in the analyses of categorical variables. *P < 0.05 (4 test) corrected with the Bonferroni principle.

### Missing data: sex, 11 (0.06%); patient source, 1552 (0.8%); NIHSS before IVT, 14686 (7.7%); thrombolytic agents, 3 (0.02%).

| Items                                      | All patients (n=192247) | Patients in secondary hospitals (n=57549) | Patients in tertiary hospitals (n=134698) | \( \chi^2 \) | P value |
|--------------------------------------------|-------------------------|------------------------------------------|------------------------------------------|--------------|---------|
| Sex, n (%)                                 | 123726 (64.36)          | 35970 (62.51)                            | 87786 (65.15)                            | 123.07       | <0.001* |
| Male                                       | 68510 (35.64)           | 21575 (37.49)                            | 46935 (34.85)                            |              |         |
| Female                                     | 186548 (97.04)          | 54945 (95.48)                            | 131603 (97.70)                           | 695.27       | <0.001* |
| Age, n (%)                                 | 67 (57.74)              | 67 (58.74)                               | 67 (57.75)                               | 0.158        |         |
| Ethnicity, n (%)                           | 5699 (2.96)             | 2604 (4.52)                              | 3095 (2.30)                              |              |         |
| Hospital Regions, n (%)                   | 7047.78                 |                                          |                                          |              |         |
| North China                                | 12930 (22.47)           | 37866 (67.90)                            | 81109 (62.42)                            | 120190 (90.08) |         |
| East China                                 | 1236 (2.17)             | 3315 (6.19)                              | 3202 (2.37)                              |              |         |
| South Central China                        | 17841 (31.00)           | 4406 (7.94)                              | 4595 (3.42)                              |              |         |
| Northeast China                            | 2451 (4.26)             | 1184 (2.17)                              | 3222 (2.34)                              |              |         |
| Southwest China                            | 9710 (16.87)            | 4406 (2.48)                              | 3222 (2.34)                              |              |         |
| Northwest China                            | 2118 (3.68)             | 1184 (2.17)                              | 3222 (2.34)                              |              |         |
| Patient source, n (%)                      | 7884.69                 |                                          |                                          |              |         |
| Ambulance to hospitals, n (%)              | 1964.74                 |                                          |                                          |              |         |
| Emergency                                  | 42764 (74.67)           | 120190 (90.08)                           | 81109 (62.42)                            |              |         |
| Outpatient department                      | 12048 (21.04)           | 10106 (7.57)                             | 3202 (2.37)                              |              |         |
| Other                                      | 2459 (4.29)             | 3222 (2.34)                              | 3222 (2.34)                              |              |         |
| NIHSS before IVT, n (%)                    | 178.27                  |                                          |                                          |              |         |
| ≤3                                        | 13549 (24.01)           | 725 (1.62)                               | 3315 (24.01)                             |              |         |
| 4−25                                      | 85922 (69.98)           | 4595 (3.42)                              | 3222 (2.34)                              |              |         |
| ≥26                                       | 55695 (41.35)           | 3222 (2.34)                              | 3222 (2.34)                              |              |         |
| DNT (min), median (interquartile range)    | 45 (33, 60)             | 45 (33, 60)                              | 45 (31, 60)                              |              |         |
| Time segments                              | 268.39                  |                                          |                                          |              |         |
| ≤30                                       | 32246 (23.94)           |                                          |                                          |              |         |
| 31−45                                     | 37908 (28.14)           |                                          |                                          |              |         |
| 46−60                                     | 31005 (23.02)           |                                          |                                          |              |         |
| >60                                       | 33539 (24.90)           |                                          |                                          |              |         |
| ONT (min), median (interquartile range)    | 168.22                  |                                          |                                          |              |         |
| ≤180                                      | 76796 (57.01)           |                                          |                                          |              |         |
| 181−270                                   | 42239 (31.36)           |                                          |                                          |              |         |
| >270                                      | 15663 (11.63)           |                                          |                                          |              |         |
| Thrombolytic agents, n (%)                 | 4920.86                 |                                          |                                          |              |         |
| rt-PA                                      | 109192 (81.87)          |                                          |                                          |              |         |
| Urokinase                                  | 24485 (18.18)           |                                          |                                          |              |         |
| Other                                      | 1018 (0.76)             |                                          |                                          |              |         |
| Complications of IVT, n (%)                |                         |                                          |                                          |              |         |
| All complications                          | 442.82                  |                                          |                                          |              |         |
| Intracranial hemorrhage                    | 14963 (11.11)           |                                          |                                          |              |         |
| Gastrointestinal bleeding                  | 4575 (3.40)             |                                          |                                          |              |         |
| Gingival bleeding                          | 922 (0.68)              |                                          |                                          |              |         |
| Bleeding in other parts                    | 1252 (0.93)             |                                          |                                          |              |         |
| Other                                      | 1226 (0.91)             |                                          |                                          |              |         |

**Table 7**: Demographic and clinical characteristics of patients receiving IVT from different grades of hospitals.

Abbreviations: DNT, door-needle-time; IVT, intravenous thrombolysis; NIHSS, National Institute of Health stroke scale; ONT, onset-needle-time; rt-PA, recombinant tissue type plasminogen activator.
### Table 2: Demographic and clinical characteristics of patients receiving EVT from different grades of hospitals.

Values are presented as numbers (percentages) or medians (interquartile range). A Mann-Whitney test was applied in the analyses of numerical variables. The χ² test was applied in the analyses of categorical variables. *P < 0.003 (n=49551) corrected with the Bonferroni principle.

| Items | All patients (n=49551) | Patients in secondary hospitals (n=2557) | Patients in tertiary hospitals (n=46994) | χ² | P value |
|-------|------------------------|------------------------------------------|-----------------------------------------|-----|---------|
| Sex, n (%) |                          |                                          |                                         | 2.95 | 0.086  |
| Male   | 31800 (64.18)           | 1600 (62.60)                             | 30200 (64.27)                           |     |         |
| Female | 17745 (35.82)           | 956 (37.40)                              | 16789 (35.73)                           |     |         |
| Age    | 66 (57.74)              | 67 (57.74)                               | 66 (57.74)                              | 0.76 | 0.766   |
| Ethnicity, n (%) |                  |                                          |                                         | 25.98 | <0.001* |
| Han    | 48299 (97.47)           | 2453 (95.93)                             | 45846 (97.56)                           |     |         |
| Minorities | 1252 (2.53) | 104 (4.07)                               | 1148 (2.44)                             |     |         |
| Hospital Regions, n (%) |            |                                          |                                         | 390.93 | <0.001* |
| North China | 4369 (8.82) | 421 (16.46)                              | 3948 (8.40)                             |     |         |
| East China | 16791 (33.89) | 729 (28.51)                             | 16062 (34.18)                           |     |         |
| South Central China | 15978 (32.25) | 916 (35.82)                               | 15062 (32.05)                           |     |         |
| Northeast China | 4216 (8.51) | 57 (2.23)                               | 4159 (8.85)                             |     |         |
| Southwest China | 5656 (11.41) | 367 (14.35)                             | 5289 (11.25)                            |     |         |
| Northwest China | 2541 (5.13) | 67 (2.62)                               | 2474 (5.26)                             |     |         |
| Patient source, n (%) |                        |                                          |                                         | 225.79 | <0.001* |
| Emergency | 41573 (85.13) | 2151 (84.59)                             | 39422 (85.16)                           |     |         |
| Outpatient department | 3069 (6.28) | 306 (12.03)                               | 2763 (5.97)                             |     |         |
| Other | 4193 (8.59)            | 86 (3.38)                                | 4107 (8.87)                             |     |         |
| Ambulance to hospitals, n (%) |                  |                                          |                                         | 175.82 | <0.001* |
| Yes | 31042 (62.65) | 1286 (50.29) | 29756 (63.32)                           |     |         |
| No | 18509 (37.35) | 1271 (49.71) | 17238 (36.68)                           |     |         |
| NIHSS before EVT |                      |                                          |                                         | 12.43 | 0.002* |
| ≤9 | 9476 (19.68)           | 549 (21.95)                              | 8927 (19.56)                            |     |         |
| 10–19 | 25193 (52.33) | 1231 (49.22)                              | 23962 (52.50)                           |     |         |
| ≥20 | 13475 (27.99)         | 721 (28.83)                              | 12754 (27.94)                           |     |         |
| DPT (min), median (interquartile range) |      |                                          |                                         | 106 (70, 161) | <0.001* |
| Time segments |                          |                                          |                                         | 164.99 | <0.001* |
| ≤90 | 20087 (40.54)          | 726 (28.39)                              | 19361 (41.20)                           |     |         |
| >90 | 29464 (59.46)          | 1831 (71.61)                             | 27633 (58.80)                           |     |         |
| OPT (min), median (interquartile range) |          |                                          |                                         | 295 (202, 415) | <0.001* |
| Time segments |                          |                                          |                                         | 107.84 | <0.001* |
| ≤200 | 12289 (24.80)         | 855 (33.44)                              | 11434 (24.33)                           |     |         |
| >200 | 37262 (75.20)         | 1702 (66.56)                             | 35560 (75.67)                           |     |         |
| Types of therapy, n (%) |                      |                                          |                                         | 301.93 | <0.001* |
| Stent retriever thrombectomy alone | 18998 (38.34) | 777 (30.39)                             | 18221 (38.77)                           |     |         |
| Thromboaspiration alone | 4106 (8.29) | 215 (8.41)                              | 3891 (8.28)                             |     |         |
| Intra-arterial thrombolytic therapy alone | 5297 (10.69) | 515 (20.14)                              | 4782 (10.18)                            |     |         |
| Stent implantation alone | 894 (1.80) | 59 (2.31)                              | 835 (1.87)                             |     |         |
| Balloon angioplasty alone | 969 (1.96) | 49 (1.92)                              | 920 (1.96)                             |     |         |
| Stent retriever embolectomy+thromboaspiration | 6653 (13.43) | 273 (10.68)                              | 6380 (13.58)                            |     |         |
| Stent retriever embolectomy+balloon angioplasty | 1389 (2.80) | 55 (2.15)                              | 1334 (2.84)                            |     |         |
| Stent retriever embolectomy+stent implantation | 1127 (2.27) | 54 (2.11)                              | 1073 (2.28)                            |     |         |
| Stent retriever embolectomy+intra-arterial thrombolytic therapy | 1350 (2.72) | 93 (3.64)                              | 1257 (2.67)                            |     |         |
| Other combinations | 8768 (17.69) | 467 (18.26)                              | 8301 (17.66)                           |     |         |
| Complications of EVT, n (%) |                          |                                          |                                         | 7216 (14.56) | 6756 (14.38) | 25.52 | <0.001* |
| All complications | 7216 (14.56) | 460 (17.99)                              | 6756 (14.38)                           |     |         |
| Intracranial hemorrhage | 3976 (8.02) | 233 (9.11)                              | 3743 (7.96)                             |     | 4.34 | 0.037 |
| Arterial dissection | 123 (0.25) | 10 (0.39)                              | 113 (0.24)                             |     | 2.23 | 0.136 |
| Occlusion | 695 (1.40) | 71 (2.78)                              | 624 (1.33)                             |     | 36.84 | <0.001* |

Abbreviations: DPT, door-puncture-time; EVT, endovascular therapy; NIHSS, National Institute of Health stroke scale; OPT, onset-puncture-time.
Figure 1. The rates of IVT and EVT for AIS in China between 2019 and 2020. (a) The overall IVT rate for AIS in China between 2019 and 2020 was 5.64%. The rate in secondary hospitals was significantly higher than that in tertiary hospitals. (b) The overall EVT rate for AIS in China between 2019 and 2020 was 1.45%. The rate in tertiary hospitals was much higher than that in secondary hospitals. *P < 0.001. Abbreviations: AIS, acute ischaemic stroke; EVT, endovascular therapy; IVT, intravenous thrombolysis.

| Articles                                                                 | Population | Study period | Participants                                                                                   | Intravenous thrombolysis rate |
|-------------------------------------------------------------------------|------------|--------------|-----------------------------------------------------------------------------------------------|-------------------------------|
| SD Reed et al. (2001)                                                   | US         | 1998–1999    | 23058 patients with ischaemic stroke from 137 community hospitals                            | 1.6% (362/23058)              |
| Schenkel et al. (2003)                                                  | Germany    | 1998–1999    | 6234 patients with ischaemic stroke from 20 stroke centers                                     | 4% (250/6234)                 |
| Arora et al. (2005)                                                     | US         | 2001–2002    | 4280 patients with ischaemic stroke from 98 hospitals                                          | 2.8% (118/4280)               |
| Zhang and Huang et al. (2009)                                           | China      | 2006         | 4783 patients with ischaemic stroke from 62 hospitals                                          | 2% (91/4783)                  |
| Eriksson et al. (2010)                                                  | Sweden     | 2003–2008    | 70705 patients with ischaemic stroke from the Swedish Stroke Register                          | 3.6% (2535/70705)            |
| Hassan et al. (2012)                                                    | US         | 2004–2009    | 3292842 patients with ischaemic stroke from a large national database                          | 2.2% (72342/3292842)         |
| Scherf et al. (2016)                                                    | Netherlands | 2005–2012    | 121887 patients with ischaemic stroke from the KNSN dataset                                     | 6.4% in 2005 and 14.6% in 2012|
| Wang et al. (2011)                                                      | China      | 2007–2008    | 11675 patients with ischaemic stroke from the CNSR                                             | 2.4% (284/11675)             |
| Rudd et al. (2011)                                                      | UK         | 2008         | 11262 acute stroke patients from the National Sentinel Stroke 2008 Audit dataset              | 1.4% (160/11262)             |
| Kim et al. (2015)                                                       | South Korea | 2008–2013    | 27851 patients with ischaemic stroke or TIA from the CRCS-5                                    | 10.7% (2973/27851)           |
| Li et al. (2016)                                                        | China      | 2007–2008    | 12173 patients with ischaemic stroke from 131 hospitals                                         | 1% (120/12173)               |
| Li et al. (2016)                                                        | China      | 2012–2013    | 19604 patients with ischaemic stroke from 219 hospitals                                         | 1.4% (243/19604)             |
| Wangqin et al. (2018)                                                   | China      | 2012–2013    | 19604 patients with ischaemic stroke from the CNSR II                                          | 2.50%                        |
| Langhorne et al. (2018)                                                 | Upper-middle-income countries | 2007–2015 | 58559 patients with ischaemic stroke from the INTERSTROKE study                               | 3% (168/5859)                |
| Weber et al. (2019)                                                     | Germany    | 2010         | 206688 patients with ischaemic stroke from the G-DRG data                                       | 8.9% (18362/206688)          |
| Weber et al. (2019)                                                     | Germany    | 2016         | 227687 patients with ischaemic stroke from the G-DRG data                                       | 14.9% (33916/227687)         |
patients receiving EVT between secondary and tertiary hospitals were more likely to be of Han ethnicity, sent to hospitals by ambulance, and admitted to tertiary hospitals. OPT were longer in 2020 than in 2019 ($b=62, 95\%CI 65-69, P<0.001$). Finally, after further adjusted for NIHSS scores before IVT, ONT, and thrombolytic agents, the overall complication rate for IVT was significantly lower in tertiary hospitals than in secondary hospitals (OR = 0.67, 95\%CI 0.65-0.70, $P<0.001$).

As shown in Figure 1 b, a significant hospital variation was also shown in the EVT rate. However, contrary to the variation in the IVT rate, a much higher EVT rate was shown in tertiary hospitals than in secondary hospitals ($1.84\%$ vs. $0.29\%, P<0.001$). As shown in Table 2, compared with AIS patients receiving EVT in secondary hospitals, those in tertiary hospitals were more likely to be of Han ethnicity, sent to hospitals by ambulance, and admitted from the emergency department.

The comparisons of clinical characteristics of patients receiving EVT between secondary and tertiary hospitals were adjusted for age, sex, ethnicity, patient source, ambulance to hospitals, and hospital regions. As shown in Table 5, patients in tertiary hospitals had significantly shorter DPT ($b=-22.96, P<0.001$) but longer OPT ($b=50.41, P<0.001$) than those in secondary hospitals. OPT were longer in 2020 than in 2019 ($b=9.62, P<0.001$) (eTable 5 in Supplementary Material). The tertiary hospitals more frequently chose stent retriever thrombectomy alone (OR = 1.21, 95\%CI 1.03-1.41, $P=0.019$) but less frequently chose intra-arterial thrombolytic therapy alone (OR = 0.39, 95\%CI 0.34-0.43, $P<0.001$) than secondary hospitals. Furthermore, after further adjusted for NIHSS scores before EVT, OPT, and types of therapy, the overall complication rate of EVT was significantly lower in tertiary hospitals than in secondary hospitals (OR = 0.69, 95\%CI 0.62-0.77, $P<0.001$).

| Studies                          | Population  | Study period | Participants                                      | Intravenous thrombolysis rate |
|----------------------------------|-------------|--------------|--------------------------------------------------|-------------------------------|
| Orite et al. (2021)$^{18}$       | US          | 2008–2017    | 4442657 patients with ischaemic stroke            | 7.0-12.3\% across the age spectrum |
|                                  |             |              | from National Inpatient Sample                    |                               |
| Aguiar de Sousa et al. (2019)$^{10}$ | 44 European countries | 2016–2017    | 1913985 patients with ischaemic stroke from 44 European countries | 7.30\%                        |
| Richter et al. (2021)$^{14}$     | Germany     | 2016         | 227687 patients with ischaemic stroke              | 14.9\% (33916/227687)         |
|                                  |             |              | from all acute care hospitals                     |                               |
| Richter et al. (2021)$^{14}$     | Germany     | 2019         | 225531 patients with ischaemic stroke              | 16.3\% (36745/225531)         |
|                                  |             |              | from all acute care hospitals                     |                               |
| The present analysis             | China       | 2019–2020    | 3408704 patients with ischaemic stroke             | 5.64\% (192247/3408704)       |
|                                  |             |              | from 1724 hospitals                               |                               |

Table 3: Thrombolysis rate for acute ischemic stroke in population-based studies.
Abbreviations: CRCS-5, Clinical Research Center for Stroke-Fifth Division; CNSR, Chinese National Stroke Registry; G-DRG, German Diagnosis-Related Groups; KNSN, Knowledge Network Stroke Netherlands; TIA, transient ischemic attack.

| Studies                          | Population  | Study period | Participants                                      | Endovascular therapy rate |
|----------------------------------|-------------|--------------|--------------------------------------------------|---------------------------|
| Weber et al. (2019)$^{27}$       | Germany     | 2016         | 227687 patients with ischaemic stroke the G-DRG data | 4.7\% (10692/227687)      |
| Smith et al. (2017)$^{26}$       | US          | 2003–2016    | 2437975 patients with ischaemic stroke from 2222 hospitals | 3.3\% in 2016            |
| Orite et al. (2021)$^{18}$       | US          | 2008–2017    | 4442657 patients with ischaemic stroke from National Inpatient Sample | 0.7–2.8\% across the age spectrum |
| Chen et al. (2019)$^{5}$         | China       | 2015         | 1826332 patients with ischaemic stroke from 1267 tertiary hospitals | 0.45\%                   |
| Aguiar de Sousa et al. (2019)$^{10}$ | 44 European countries | 2016–2017    | 1913985 patients with ischaemic stroke from 44 European countries | 1.90\%                   |
| Richter et al. (2021)$^{14}$     | Germany     | 2016         | 227687 patients with ischaemic stroke              | 4.3\% (9795/227687)       |
|                                  |             |              | from all acute care hospitals                     |                           |
| Richter et al. (2021)$^{14}$     | Germany     | 2019         | 225531 patients with ischaemic stroke              | 7.2\% (16135/225531)      |
|                                  |             |              | from all acute care hospitals                     |                           |
| The present analysis             | China       | 2019–2020    | 3408704 patients with ischaemic stroke             | 1.45\% (49551/3408704)    |
|                                  |             |              | from 1724 hospitals                               |                           |

Table 4: Endovascular therapy rate for acute ischemic stroke in population-based studies.
Abbreviations: CRCS-5, Clinical Research Center for Stroke-Fifth Division; G-DRG, German Diagnosis-Related Groups.
### Table 5: Multivariable regression models to compare characteristics of patients from different grades of hospitals.

Values are presented as OR (95% CI) for categorical dependent variables and β ± SE for continuous dependent variables. All models were adjusted for age, sex, ethnicity, patient source, ambulance to hospitals, and hospital regions. *Additionally adjusted for NIHSS scores before EVT, OPT, and types of therapy. §Additionally adjusted NIHSS scores before IVT, ONT, and thrombolytic agents.

**Abbreviations:** β, regression coefficients; CI, confidence interval; DNT, door-needle-time; DPT, door-puncture-time; EVT, endovascular therapy; IVT, intravenous thrombolysis; NIHSS, National Institute of Health stroke scale; ONT, onset-needle-time; OPT, onset-puncture-time; OR, odds ratios; rt-PA, recombinant tissue type plasminogen activator; SE, standard error.

| Items | Tertiary vs. secondary hospitals |
|-------|---------------------------------|
|       | OR (95%CI) or β ± SE | P value |
| **Patients Receiving IVT** | | |
| NIHSS before IVT | | |
| 4–25 vs. ≤3 | 0.80 (0.78–0.82) | <0.001 |
| ≥26 vs. ≤3 | 0.91 (0.84–0.97) | 0.009 |
| DNT (min) | –0.31 ± 0.17 | 0.074 |
| ≤30 vs. >60 | 1.15 (1.12–1.19) | <0.001 |
| 31–45 vs. >60 | 0.93 (0.90–0.95) | <0.001 |
| 46–60 vs. >60 | 0.88 (0.86–0.91) | <0.001 |
| ONT (min) | 8.67 ± 0.39 | <0.001 |
| ≤180 vs. >270 | 0.80 (0.77–0.83) | <0.001 |
| 181–270 vs. >270 | 1.02 (0.99–1.06) | 0.232 |
| Thrombolytic agents, n (%) | | |
| rt-PA vs. urokinase | 2.16 (2.1–2.21) | <0.001 |
| Other vs. urokinase | 0.10 (0.90–1.10) | <0.001 |
| Complications of IVT, n (%) | | |
| All complications | 0.67 (0.65–0.70) | <0.001 |
| Intracranial hemorrhage | 1.00 (0.94–1.06) | 0.750 |
| Gastrointestinal bleeding | 1.17 (1.01–1.34) | 0.018 |
| Gingival bleeding | 0.56 (0.54–0.58) | <0.001 |
| Bleeding in other parts | 0.70 (0.63–0.77) | <0.001 |
| Other | 0.80 (0.72–0.89) | <0.001 |
| Patients Receiving EVT | | |
| NIHSS before EVT | | |
| 10–19 vs. ≤9 | 1.17 (1.05–1.30) | 0.004 |
| ≥20 vs. ≤9 | 1.01 (0.90–1.13) | 0.917 |
| DPT (min) | –2.26 ± 1.91 | <0.001 |
| ≤90 vs. >90 | 1.67 (1.52–1.82) | <0.001 |
| OPT (min) | 50.41 ± 4.59 | <0.001 |
| ≤200 vs. >200 | 0.65 (0.60–0.71) | <0.001 |
| Types of therapy, n (%) | | |
| Thromboaspiration alone | ref | | |
| Stent retriever thrombectomy alone | 1.21 (1.03–1.41) | 0.019 |
| Intra-arterial thrombolytic therapy alone | 0.39 (0.34–0.43) | <0.001 |
| Stent implantation alone | 0.65 (0.49–0.86) | 0.111 |
| Balloon angioplasty alone | 0.84 (0.62–1.13) | 0.954 |
| Stent retriever embolectomy+thromboaspiration | 1.01 (0.88–1.17) | 0.033 |
| Stent retriever embolectomy+balloon angioplasty | 1.01 (0.77–1.34) | 0.195 |
| Stent retriever embolectomy+stent implantation | 0.85 (0.64–1.13) | 0.868 |
| Stent retriever embolectomy+intra-arterial thrombolytic therapy | 0.63 (0.50–0.79) | 0.035 |
| Other combinations | 0.79 (0.70–0.89) | 0.550 |
| Complications of EVT, n (%) | | |
| All complications | 0.69 (0.62–0.77) | <0.001 |
| Intracranial hemorrhage | 0.77 (0.67–0.90) | <0.001 |
| Arterial dissection | 0.54 (0.28–1.05) | 0.070 |
| Re-occlusion | 0.43 (0.33–0.55) | <0.001 |
Discussion

In this analysis, we found that the overall IVT and EVT rates in China between 2019 and 2020 were 5.64% and 1.45%, respectively. The IVT rate in secondary hospitals was higher than that in tertiary hospitals, whereas the EVT rate in secondary hospitals was much lower than that in tertiary hospitals. Although the rates of IVT and EVT in China have increased in recent years, there is still a large gap compared with developed countries.

From previous studies, we observed an increase in the IVT rate in China from 2% in 2006, 1~2.4% in 2007~2008, and 1.4~2.5% in 2012~2013 to 5.64% in 2019~2020 in the present analysis. These data prove the substantial improvement of acute stroke care in China during the past decades. A recent study by Zhao et al. also based on the BOSC showed much higher rates of IVT in China, i.e., 7.8% in February 2019 and 9.4% in February 2020, than did the present analysis. This may be because the study by Zhao et al. used a different methodology in data acquisition and covered 280 highly selected hospitals that might perform well on IVT. Notably, the IVT rate in China is still much lower than that in developed countries. The IVT rate was 11.7~18.2% in the US in 2017 and 16.5% in Germany in 2019. There are still big challenges for IVT in China.

Previous studies showed that the DNT decreased from 116 min in 2007~2008 to 95 min in 2012~2013 and 49 min in 2018. This analysis demonstrated that the median DNT was 45 min between 2019 and 2020, and 75.43% of patients were treated within 60 min. A DNT less than 60 min is a key quality index of stroke management defined by the CSPPC, and the quality of stroke management of each stroke centre is ranked on the website every month to optimize the process of stroke treatment. For the therapeutic options for IVT, a large proportion of patients (52.32% for secondary hospitals and 81.8% for tertiary hospitals) were treated with urokinase in China. This situation is different from that in European and American countries, where urokinase is usually not licenced for use in IVT.

In 2001, urokinase was proven to be effective and safe for ischemic stroke patients within 6 h of onset by a trial performed in China. Thus, Chinese guidelines for the diagnosis and treatment of acute ischemic stroke recommend urokinase for intravenous thrombolysis for AIS. As urokinase is much less expensive than rt-PA and has a wider time window for IVT, it is popular in secondary hospitals that cover more rural areas in China.

Unexpectedly, our analysis demonstrated that the IVT rate in secondary hospitals was significantly higher than that in tertiary hospitals (6.39% vs. 5.39%). A possible explanation is that although tertiary hospitals are much better equipped with advanced infrastructure and a professional medical team, secondary hospitals are more likely to receive acute onset patients before referring to tertiary hospitals. The proportion of short DNT (≤30 min) in tertiary hospitals was higher than that in secondary hospitals, but the ONT in tertiary hospitals was longer than that in secondary hospitals, possibly reflecting a longer prehospital delay and a higher proportion of late-presenting patients in tertiary hospitals. A recent study in northeast Thailand showed that community hospitals had shorter ONT for rt-PA treatment than regional hospitals and tertiary hospitals. Other studies also showed that a referral was associated with prehospital delay.

In 2015, mechanical thrombectomy became an evidence-based treatment based on five randomized trials showing the safety and efficacy of thrombectomy with stent retrievers in patients with large vessel occlusion. Then, the Chinese guidelines for EVT for AIS 2015 were established to provide quality control norms for EVT. The EVT rate in tertiary hospitals was only 0.43% in 2015, but the rate increased to 1.84% between 2019 and 2020. The US and Germany also showed a similar trend. Our analysis revealed that approximately 95% of EVTs for AIS were performed in tertiary hospitals. To date, secondary hospitals have limited access to neurological intervention centres, and most patients are referred to high-level hospitals to obtain a thrombectomy-capable facility. Therefore, although the DPT was shorter in tertiary hospitals than in secondary hospitals (105 min vs. 129 min), the OPT was much longer in tertiary hospitals (300 min vs. 250 min). This emphasizes the need to develop a region-specific network for stroke treatment, and an improvement in the division of labor for stroke treatment between secondary and tertiary hospitals should be taken into consideration.

Both the overall complication rates for IVT and for EVT were significantly lower in tertiary hospitals than in secondary hospitals, although both ONT and OPT were longer in tertiary hospitals than in secondary ones. This suggested an inhomogeneity in medical level between tertiary and secondary hospitals. It is necessary to implement training and accreditation for acute stroke management, and to improve the quality of IVT in secondary hospitals. Considering the better accessibility and lower complication rate of EVT in tertiary hospitals, eligible patients could be directly diverted to tertiary hospitals.

This analysis was based on the most recent data derived from the BOSC, which provided national and up-to-date evidence of AIS care in China. However, this analysis also had several limitations. First, the database mainly covered hospitals with stroke centres, and these hospitals could provide better stroke management than those not covered by the database. The rates of IVT and EVT in the latter and the overall rates in China might be lower than the present data. Nevertheless, to date, the present analysis has the widest coverage range in China. Second, the present analysis did not have detailed information on patients not receiving IVT/EVT, and thus,
the factors affecting the utilization of IVT and EVT and the differences in the characteristics of all AIS patients between tertiary and secondary hospitals were not known. A sampling system for all patients with AIS (receiving or not receiving IVT/EVT) would be helpful to solving this problem. Third, some information on referrals of AIS patients to high-level hospitals for EVT was incomplete. Some of them received IVT before referrals, but the detailed information on IVT of these patients might be incomplete. To solve this situation, a hospital information sharing system is under construction. Forth, the data in the present analysis were self-reported by hospitals. Although a series of initiatives were performed to control the quality of the data, the accuracy might be questionable. More efforts, e.g., sampling inspection and an automated data reporting system, would be made to improve the quality. Finally, although both the IVT and EVT rates were significantly higher in 2020 than in 2019, the rates in 2020 might be overestimated. This is because, in China, there was a larger drop in hospital admissions for stroke than in IVT and EVT cases during the height of the epidemic of coronavirus disease 2019 in early 2020.17

In conclusion, the rates of IVT and EVT for AIS have greatly increased in China, but there is still a large gap compared with developed countries. Tertiary hospitals had a much higher EVT rate but a lower IVT rate than secondary hospitals. These findings have important implications for acute stroke management and may assist in developing a region-specific network for stroke treatment in China.

Contributors
LDW contributed to the conceptualization and project administration. YCZ contributed to the data interpretation, methodology, and writing-review & editing. QY contributed to the data analysis, formal analysis, methodology, writing-original draft, and manuscript revision. FZ contributed to the data analysis, methodology, and writing-original draft. BC contributed to the project administration, resources, software, data curation, and verifying the underlying data. LC contributed to the investigation, formal analysis, methodology, supervision, validation, data curation, and verifying the underlying data. YX contributed to the formal analysis, methodology, and data collection. PZ, HH, LW, BX, WC, CW, SW, RW, LZ, LJ, and SL contributed to data collection. All authors reviewed and approved the manuscript.

Data sharing statement
All relevant data from the present study are included in the article. Other deidentified data are available from the corresponding author upon reasonable request following the publication of this article.

Declaration of interests
We declare no competing interests.

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Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jlanwpc.2022.100406.

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