Treatment Patterns of Newly Diagnosed Asthma Patients in an Urban Setting in China: A Retrospective Longitudinal Real World Evidence Study

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Research

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Abstract

Background: Asthma is prevalent but largely undiagnosed and undertreated in China. Despite readily available effective therapies, the outcomes still leave much to be desired. There is a scarcity of data describing the treatment patterns of patients with newly diagnosed asthma in real world settings. The main goal of this study was to investigate treatment patterns of newly diagnosed asthma patients with up to 1 year follow-up to gain a better understanding of gaps of optimal asthma management in China.

Methods: We conducted a large-scale of retrospective cohort analysis of asthma treatment for newly diagnosed patients using an electronic medical record database (SuValue). Eligible patients were at least 14 years old at the diagnosis from 2001 to March 2019. We categorized anti-asthmatic medication use by its classes and documented their use by the underlying disease severity. To examine the use of controlled medications over follow-ups, we summarized their utilization over consecutive 3-month time windows from the initial diagnosis to the end of follow-up.

Results: A total of 26,301 patients from tertiary (25.24%), secondary (71.83%) and primary (2.92%) hospitals were included in the study; 54.01% received one or more controller medications during the study period and 30.4% had 12 months of follow-up visits. Initial prescriptions were inhaled corticosteroid (ICS)-containing controller treatment (13.9%), other controller treatment (31.59%), anti-asthmatic relivers (23.76%), symptomatic medications (14.54%) and no medication (16.2%). Patients mostly discontinued their controller prescriptions within 6 months after the initial diagnosis. Of the 45.98% patients not receiving any controller medication, 70.16% used relivers or symptomatic medications during follow-up visits. In patients who had 12-month follow-up visits, 76.86%, 17.25%, 5.88% were deemed to have mild, moderate, and severe asthma, respectively, during the 1st 3 months. Percentages of severe and moderate asthma patients were halved by the 2nd 3-month landmark and remained stable over the remaining follow-up visits. There were significant differences in asthma treatment between tertiary and secondary hospitals.

Conclusion: In newly diagnosed asthma patients, controller medications were significantly underused while symptom-relief drugs, on the other hand, appeared to be overused. Poor adherence to current guidelines were common and more noticeable in lower tiered hospitals. These findings call for needs of more aggressive asthma management and more educational efforts in China.

1. Introduction

Asthma is prevalent but largely undiagnosed and undertreated afflicting 47.5 million adults in China and it is crucial to increase the awareness of asthma and disseminate standardised treatment in clinical settings to reduce the disease burden [1]. The Global Initiative for Asthma (GINA) recommends that treatment should be initiated as soon as the diagnosis is made with regular clinical follow-up visits to review and adjust the treatment for optimal therapy adherence and compliance[2]. Inhaled corticosteroid (ICS)-containing medications are recommended as the preferred asthma controller for all patients from mild to severe asthma[3][4][5][6][7]. Other options of the controllers such as leukotriene receptor antagonist (LTRA) alone or with ICS[8][9][10][11][12], long-acting muscarinic antagonist (LAMA) with ICS-LABA before stepping up to biologics[13][14] and/or low-dose maintenance oral corticosteroid (OCS), theophylline, and mast cell stabilizer (MCS) like sodium cromoglicate, are also mentioned in the local practice guideline as standardised treatment [15]. Despite the availability of effective therapies, national and international surveys continue to reveal inadequate asthma control in more than 50% of patients [16][17][18]. In China, findings from a recent multi-center, cross-sectional survey showed that adequate asthma control in urban area of China was 28.5%, which was nearly identical to 28.7% from previous asthma control survey in 2008 [19]. Another large scale population-based survey found 15.5% people with asthma reported at least one emergency room visit and 7.2% at least one hospital
admission due to exacerbation of respiratory symptoms within the preceding year [1]. These findings highlight a critical need to understand gaps to asthma management in practice.

Poor adherence to regular maintenance medication is a reality in asthma [20]. The commonly observed pattern is the use of medication only when symptoms occur and avoidance of treatment when it is perceived to be unnecessary [21]. To date, no available data in China have examined treatment patterns of patients with newly diagnosed asthma in real world settings. We aimed to document treatment journeys by examining a retrospective cohort of newly diagnosed asthma patients by analysing a large electronic health record database. We focused our analyses on the initial therapies and clinical pathways of patients who were adherent to their follow up visits in order to further understand therapy changes in relation to the underlying disease severities.

2. Methods

2.1 Data Source

SuValue health information database is a structured electronic hospital medical record system constructed and based on ambulatory and hospitalization encounters with de-identified patient level data of all diseases in real-world settings. The database captures the full continuum of treatment information for more than 90 million patients from 207 hospitals, 18 provinces in China. The patient level data can be longitudinally tracked, including demographics, diagnosis, lab results, prescriptions, procedures, and costs for inpatient, outpatient, and emergency room care. The database was constructed and shared for research purpose with full authorization of each participating hospital. Centennial Scientific Co. Ltd. has dedicated access to the SuValue database.

2.2 Patients and Study Design

This was a retrospective cohort study on newly diagnosed asthma patients. Eligible patients were at least 14 years old at the initial diagnosis (ICD-10-CM: J45) (index date) from 2001 to March 2019 and had at least two non-asthma related clinic visits separated by at least 30 days over the 1-year pre-index period to ensure the continuity of care [22]. Patients were followed from the initial diagnosis to either being censored or longest data available in 12 months (Figure 1). Censoring was defined as a patient not having an all-cause clinical visit recorded in SuValue database since last visit for at least 6 months [23].

This study was designed, implemented, and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [24]. As we only used existing data and all personally identifiable information was removed by the database provider prior to receipt by the study team, neither informed patient consent nor institutional review board/ethics committee approval is required per the local medical research policy for using electronic health records.

2.3 Baseline Characteristics and Outcome Measurement

Patient characteristics such as demographics and prescriptions received at the index date were evaluated and analysed.

The outcome measure - treatment patterns of anti-asthmatic medication usage (controllers and relievers) were assessed from the initial diagnosis to the end of follow-up. The proportion of patients on different controllers and therapies was reported. Controller medication use and asthma severity classification were summarized for each consecutive 3-month
time window as Observation Window Unit (OWU) from the index date to the end of follow-up. We applied a drug-based severity classification method for this study according to GINA 2018 stepwise treatment recommendation[25]. 1-month grace period before and after the OWU was permitted to account for patients’ early or late visit. In situations in which multiple controller therapies were recorded for a given OWU, asthma severity classification was based on the last prescription of controller medication (category and dosage) for this OWU.

2.4 Statistics Analysis

Descriptive data were reported as means ± SD or percentages as appropriate. Baseline characteristics of patients were presented as counts (n) and proportions (%); summary statistics were presented for continuous data. Subgroup analysis was carried out among the subsets of population with the index asthma visits from the hospitals of different tiers to compare their treatment patterns by using the Chi-square /Fisher exact test. The unequal variance two-sample t-test was used for continuous data. Two-tailed P values were reported.

3. Results

3.1 Study Population and Patient Characteristics

Of the total 26,301 newly diagnosed asthma patients, 14,207 (54.01%) patients received treatment of one or more controller medications and the remaining 12,094 (45.98%) patients did not receive any controllers during the study period. Following the initial diagnosis, 9,166 patients had at least 3-month follow-up visits and 7,996 patients had continuous care by the end of 12 months (Figure 2). Table 1 displays number of patients entered into the study cohort by year from 2001 to March 2019. Vast majority of patients were diagnosed in secondary (71.8%) or tertiary (25.2%) hospitals on the index date. Patient demographic characteristics are presented in Table 2.
Table 1. Patient characteristics

|                          | Total       | With controller medication prescriptions over the study period | With 12-month follow-up |
|--------------------------|-------------|-------------------------------------------------------------|-------------------------|
|                          | N=26,301    | N=14,207                                                    | N=7,996                 |
| Gender, n (%)            |             |                                                             |                         |
| males                    | 11,651      | 44.30%                                                      | 3,621                   |
|                          |             | 44.13%                                                      | 45.29%                  |
| females                  | 14,397      | 54.74%                                                      | 4,281                   |
|                          |             | 54.73%                                                      | 53.54%                  |
| Unidentified             | 253         | 0.96%                                                       | 94                      |
|                          |             | 1.14%                                                       | 1.18%                   |
| Age, years, mean (SD)    | 48(17.05)   | 49(16.51)                                                   | 52(17.08)               |
| 14-39                    | 8,699       | 33.07%                                                      | 2,110                   |
|                          |             | 30.63%                                                      | 26.39%                  |
| 40-60                    | 10,016      | 38.08%                                                      | 2,875                   |
|                          |             | 39.73%                                                      | 35.96%                  |
| >60                      | 7,586       | 28.84%                                                      | 3,011                   |
|                          |             | 29.64%                                                      | 37.66%                  |
| Hospital, n (%)          |             |                                                             |                         |
| Tertiary                 | 6,639       | 25.24%                                                      | 2,019                   |
|                          |             | 31.37%                                                      | 25.25%                  |
| Secondary                | 18,893      | 71.83%                                                      | 5,635                   |
|                          |             | 66.41%                                                      | 70.47%                  |
| Primary                  | 769         | 2.92%                                                       | 342                     |
|                          |             | 2.22%                                                       | 4.28%                   |

3.2 Treatment

3.2.1 Initial Treatment

On the index date, a total of 26,301 patients were diagnosed with asthma from various departments, in descending order, respiratory (26.54%), internal medicine (24.39%), emergency (16.62%), general medicine (14.21%), Chinese medicine (8.74%), etc (Table 3). There were significant differences in department distribution between tertiary and secondary hospitals.

At the initial diagnosis, 11,965 (45.49%) patients received controller medications, 6,249 (23.76%) received anti-asthmatic reliever only, 3,825 (14.54%) received symptomatic medications, e.g. antitussives, mucolytics or antibiotics, and 4,262 (16.2%) received no prescription of medications. In patients receiving controller therapies, corticosteroid-containing and leukotriene receptor antagonist (LTRA) were most commonly prescribed with 4,564 (38.14%) and 3,359 (28.07%) patients, respectively. Other less frequently used controller medications included xanthine derivatives (15.8%) and others (17.98%), e.g., mast cell stabilizers (MCS), etc. Among 4,433 (18.0%) patients with LTRA prescriptions, LTRA only, combination of corticosteroid and combination of other controllers were 2,225 (47.01%), 1,374 (29.3%) and 1,134 (23.96%), respectively. Among 4,359 (16.57%) patients with short-acting β2-agonist (SABA) treatment, 2,327 (53.28%) were in combination use with the controllers. There were significant differences in all prescriptions, including LTRA and SABA between tertiary and secondary hospitals at the initial asthma diagnosis.

Table 3. Treatment received at the initial asthma diagnosis
### Department, n, %

| Department                        | All Hospitals N=26301 (100%) | Tertiary Hospitals N=6,639 (25.24%) | Secondary Hospitals N=18,893 (71.83%) | Primary Hospitals N=769 (2.92%) | Tertiary vs. Secondary P value |
|-----------------------------------|------------------------------|------------------------------------|---------------------------------------|---------------------------------|------------------------------|
| Respiratory                       | 6979 26.54%                  | 3558 53.59%                        | 3340 17.68%                          |                                 | <0.001                      |
| Internal medicine                 | 6416 24.39%                  | 1112 16.75%                        | 5426 28.72%                          |                                 |                              |
| Emergency                         | 4370 16.62%                  | 445 6.70%                          | 3925 20.77%                          |                                 |                              |
| General medicine                  | 3737 14.21%                  | 590 8.89%                          | 2329 12.33%                          | 752 97.79%                      |                              |
| Chinese medicine                  | 2300 8.74%                   | 375 5.65%                          | 1950 10.32%                          |                                 |                              |
| Otolaryngology                    | 1421 5.40%                   | 146 2.20%                          | 1275 6.75%                           |                                 |                              |
| Surgical                          | 405 1.54%                    | 139 2.09%                          | 266 1.41%                            |                                 |                              |
| Pediatric                         | 365 1.39%                    | 204 3.07%                          | 162 0.86%                            |                                 |                              |
| Obstetrics and Gynecology         | 74 0.28%                     | 32 0.48%                           | 41 0.22%                             |                                 |                              |
| Unidentified                      | 234 0.89%                    | 38 0.57%                           | 179 0.95%                            | 17 2.21%                        |                              |

### All prescriptions N=26,301

| Controller, n, % | 11,965 45.49% | 4,032 60.73% | 7,717 40.85% | 216 28.09% | <0.001 |
|------------------|---------------|--------------|--------------|-----------|--------|
| OCS containing   | 908 3.5%      | 211 3.18%    | 671 3.55%    | 26 3.38%  |        |
| ICS-LABA containing | 3,148 12.0% | 1,585 23.87% | 1,563 8.27% |           | <0.001 |
| ICS containing   | 508 1.9%      | 149 2.24%    | 359 1.90%    |           |        |
| LTRA containing  | 3,359 12.8%   | 1,309 19.72% | 2,049 10.85% | 1 0.13%   |        |
| Theophylline containing | 1,891 7.2% | 411 6.19%    | 1,380 7.30%  | 100 13.00% |        |
| Others (MCS etc.) | 2,151 8.2%   | 367 5.53%    | 1,695 8.97%  | 89 11.57% |        |
| Anti-asthmatic relievers, n, %    | 6,249 23.76% | 837 12.61%  | 5113 27.06% | 299 38.88% |        |
| SABA containing    | 2,032 7.7%    | 327 4.93%    | 1,633 8.64%  | 72 9.36%  |        |
| Other anti-asthmatic relievers   | 4,217 16.0%   | 510 7.68%    | 3,480 18.42% | 227 29.52% |        |
| Symptomatic medications, n, %    | 3,825 14.54%  | 861 12.97%   | 2,826 14.96% | 138 17.95% |        |
| No prescription, n, %             | 4,262 16.20%  | 909 13.69%   | 3,237 17.13% | 116 15.08% |        |

### LTRA Prescription N=4,733 (18.00%)

| Corticosteroid, n, % | 1,374 29.03% | 541 11.43% | 833 17.6% | - | - | <0.001 |
| OCS combination      | 324 6.85%    | 64 1.35%   | 260 5.49% | - | - |        |
| Combination                          | n     | 19.54% | 9.76% | 9.78% | 2.32% | 16.23% |
|-------------------------------------|-------|--------|-------|-------|-------|--------|
| ICS-LABA combination               | 925   |        |       |       |       |        |
| ICS combination                     | 125   | 2.64%  | 0.32% |       |       |        |
| Other controllers, n, %             | 1,134 | 23.96% | 7.73% |       |       |        |
| Theophylline combination            | 556   | 11.75% | 3.06% |       |       |        |
| Others (MCS etc.)                   | 578   | 12.21% | 4.67% | 7.54% |       |        |
| LTRA only, n, %                     | 508   | 10.73% | 4.80% | 5.92% | 1     | 0.02%  |
| Other anti-asthmatic relievers, n, %| 887   | 18.74% | 6.53% | 12.21%|       |        |
| Symptomatic medications, n, %      | 830   | 17.54% | 8.60% | 8.94% |       |        |

**SABA Prescription N=4,359 (16.57%)**

| Combination                          | n     | 53.38% | 14.87% | 38.17% | 0.34% | <0.001 |
|-------------------------------------|-------|--------|--------|--------|-------|--------|
| Controller, n, %                    | 2,327 |        |        |        |       |        |
| OCS combination                      | 50    | 1.15%  | 0.14%  | 0.94%  | 3     | 0.07%  |
| ICS-LABA combination                | 564   | 12.94% | 5.48%  | 7.46%  |       |        |
| ICS combination                      | 161   | 3.69%  | 0.55%  | 3.14%  |       |        |
| LTRA combination                    | 741   | 17.00% | 6.31%  | 10.69% |       |        |
| Theophylline combination             | 365   | 8.37%  | 1.24%  | 7.02%  | 5     | 0.11%  |
| Others (MCS etc.)                   | 446   | 10.23% | 1.15%  | 8.92%  | 7     | 0.16%  |
| SABA only, n, %                     | 367   | 8.42%  | 1.56%  | 6.79%  | 3     | 0.07%  |
| Other anti-asthmatic relievers, n, %| 1,395 | 32.00% | 5.39%  | 25.46% | 50    | 1.15%  |
| Symptomatic medications, n, %      | 270   | 6.19%  | 0.55%  | 5.21%  | 19    | 0.44%  |

Note:
1. Patient was categorized by the highest preferred treatment of each step from GINA 2018, e.g. categorized as OCS if use combination of OCS and ICS-LABA, without overlapping counting in every category.
2. Other anti-asthmatic relievers included SAMA, SABA/SAMA combination, short-acting xanthine derivatives, short course (≤7 days) injective/oral/nebulized corticosteroids
3. Symptomatic medications included TCM, antitussive, mucolytics, cough-mucolytics combination, anti-histamine, antibiotics

OCS: Oral corticosteroid; ICS-LABA: Inhaled corticosteroid and long-acting β2-agonist combination; ICS: Inhaled corticosteroid; LTRA: Leukotriene receptor antagonist; MCS: Mast cell stabilizers; SABA: short-acting β2-agonist; TCM: Traditional Chinese medicine

3.2.2 Changes in Asthma Treatment

3.2.2.1 Adherence to Follow-up Hospital Visits
Overall, 7,996 (30.4%) of 26,301 newly diagnosed asthma patients received continuous care for 12 months. Among them, 5,109 (63.89%) had at least one controller medication prescription over the follow-up period and 2,887 (36.11%) patients were not treated with any controller medication.

Among 14,207 patients with controller medication prescriptions, it’s appeared to be similar proportions of patients who lost to follow-up by end of each 3-month OWU (Figure 3 A1). The trends in tertiary, secondary and primary hospitals were similar (Figure 3 B1, C1, D1).

### 3.2.2.1 Controller Medication Pattern

Among 14,207 patients receiving treatment of controller medications during the study period, treatment pattern of controllers was examined in each 3-month OWU by different tiers of hospitals (Figure 3).

On index date and over 1st 3-month OWU, respectively, the most common prescriptions were ICS-containing, including ICS and ICS-LABA (25.73% and 32.08%), LTRA-containing (23.64% and 23.01%), others (15.14% and 15.40%) and theophylline-containing (13.31% and 13.63%). Over 2nd to 4th 3-month OWUs, respectively, the most common options were no controller prescription (77.35%, 79.86% and 79.04%), ICS-containing (10.17%, 9.8% and 9.81%) and LTRA-containing (4.21%, 3.62% and 3.44%) (Figure 3 A2).

Among patients treated in tertiary hospitals, on the index date and over 1st 3-month OWU, ICS-containing medications were prescribed in 38.91% and 46.26% patients, respectively; LTRA-containing were used in 29.37% and 27.32% patients, respectively. Over 2nd to 4th 3-month OWUs, no controller were prescribed in 79.76%, 81.46% and 80.04% of patients, respectively and ICS-containing was used in 13.16%, 12.07% and 12.75%, respectively. (Figure 3 B2). Among patients treated in secondary hospitals, the most common prescriptions were LTRA-containing (21.72%), ICS-containing (20.37%), no controller use (18.21%) at diagnosis; ICS-containing (26.9%), LTRA-containing (22.19%), others (17.02%) over 1st 3-month OWU; and no controller prescriptions (76.15%, 79.06% and 78.47%), ICS-containing (9.16%, 8.82% and 8.86%) over 2nd to 4th 3-month OWUs, respectively (Figure 3 C2). Among patients treated in primary hospitals, the most common prescriptions were no controller use, theophylline-containing and MCS-containing treatment (Figure 3 D2).

Many patients discontinued controller prescriptions over the follow-up visits and discontinuation of controller medication was most common in patients with mild asthma and occurred within first 6 months of the initial diagnosis. Among 7,315 patients having at least two OWUs follow-up visits, 64.17%, 28.14% and 7.68% patients with mild, moderate and severe asthma in 1st 3-month OWU discontinued controller prescription in 2nd OWU, respectively. Among 6,074 patients having at least three 3-month OWUs follow-up visits, 57.5%, 33.33% and 9.17% patients with mild, moderate and severe asthma in 2nd 3-month OWU discontinued controller prescriptions in 3rd 3-month OWU, respectively.

For all prescriptions, there were significant differences in prescription types between tertiary and secondary hospitals (Table 4).

### Table 4 Treatment pattern in patients received controller medications during the study period
| Index date | ALL | Tertiary Hospitals | Secondary Hospitals | Primary Hospitals | Tertiary vs. Secondary |
|------------|-----|--------------------|---------------------|------------------|-----------------------|
|            | N=14,207 (100%) | N=4,457 (31.37%) | N=9,435 (66.41%) | N=315 (2.22%) | P value |
| Controller, n, % | 11,965 84.22% | 4,032 90.46% | 7,717 81.79% | 216 68.57% | <0.001 |
| OCS containing | 908 6.39% | 211 4.73% | 671 7.11% | 26 8.25% | |
| ICS-LABA containing | 3,148 22.16% | 1,585 35.56% | 1,563 16.57% | 0 0.00% | 0.00% |
| ICS containing | 508 3.58% | 149 3.34% | 359 3.80% | 0 0.00% | |
| LTRA containing | 3,359 23.64% | 1,309 29.37% | 2,049 21.72% | 1 0.32% | |
| Theophylline containing | 1,891 13.31% | 411 9.22% | 1,380 14.63% | 100 31.75% | |
| Others (MCS etc.) | 2,151 15.14% | 367 8.23% | 1,695 17.97% | 89 28.25% | |
| No Controller, n, % | 2,242 15.78% | 425 9.54% | 1,718 18.21% | 99 31.43% | |

| OWU1 | N=9,166 (100%) | N=2,914 (34.79%) | N=5,918 (64.56%) | N=234 (2.55%) | |
| Controller, n, % | 8,605 93.88% | 2,821 96.81% | 5,501 92.95% | 183 78.21% | <0.001 |
| OCS containing | 895 9.76% | 191 6.55% | 672 11.36% | 32 13.68% | |
| ICS-LABA containing | 2,519 27.48% | 1,238 42.48% | 1,281 21.65% | 0 0.00% | |
| ICS containing | 421 4.59% | 110 3.77% | 311 5.26% | 0 0.00% | |
| LTRA containing | 2,109 23.01% | 796 27.32% | 1,313 22.19% | 0 0.00% | |
| Theophylline containing | 1,249 13.63% | 253 8.68% | 917 15.50% | 79 33.76% | |
| Others (MCS etc.) | 1,412 15.40% | 233 8.00% | 1,007 17.02% | 72 30.77% | |
| No Controller, n, % | 561 6.12% | 93 3.19% | 417 7.05% | 51 21.79% | |

| OWU2 | N=7,315 (100%) | N=2,302 (31.47%) | N=4,813 (65.80%) | N=200 (2.73%) | |
| With Controller, n, % | 1,657 22.65% | 466 20.24% | 1,148 23.85% | 43 21.50% | <0.001 |
| Drug Class                  | N  | %    |  N  | %    |  N  | %    |  N  | %    |
|----------------------------|----|------|----|------|----|------|----|------|
| OCS containing             | 206| 2.82%| 36 | 1.56%| 162| 3.37%| 8  | 4.00%|
| ICS-LABA containing        | 648| 8.86%| 283| 12.29%| 365| 7.58%| 0  | 0.00%|
| ICS containing             | 96 | 1.31%| 20 | 0.87%| 76 | 1.58%| 0  | 0.00%|
| LTRA containing            | 308| 4.21%| 81 | 3.52%| 227| 4.72%| 0  | 0.00%|
| Theophylline containing     | 209| 2.86%| 26 | 1.13%| 162| 3.37%| 21 | 10.50%|
| Others (MCS etc.)          | 190| 2.60%| 20 | 0.87%| 156| 3.24%| 14 | 7.00%|
| **No Controller, n, %**    | 5,658| 77.35%| 1,836| 79.76%| 3,665| 76.15%| 157| 78.50%|
| **OWU3**                  |    |      |    |      |    |      |    |      |
| Controller, n, %           | 1,223| 20.14%| 347| 18.54%| 838| 20.94%| 22 | 11.96%| <0.001|
| OCS containing             | 127 | 2.09%| 25 | 1.34%| 98 | 2.45%| 4  | 2.17%|
| ICS-LABA containing        | 514 | 8.46%| 226| 12.07%| 288| 7.20%| 0  | 0.00%|
| ICS containing             | 81 | 1.33%| 0  | 0.00%| 65 | 1.62%| 0  | 0.00%|
| LTRA containing            | 220 | 3.62%| 61 | 3.26%| 159| 3.97%| 0  | 0.00%|
| Theophylline containing     | 147 | 2.42%| 17 | 0.91%| 121| 3.02%| 9  | 4.89%|
| Others (MCS etc.)          | 134 | 2.21%| 18 | 0.96%| 107| 2.67%| 9  | 4.89%|
| **No Controller, n, %**    | 4,851| 79.86%| 1,525| 81.46%| 3,164| 79.06%| 162| 88.04%|
| **OWU4**                  |    |      |    |      |    |      |    |      |
| Controller, n, %           | 1,071| 20.96%| 321| 19.96%| 719| 21.53%| 31 | 19.14%| <0.001|
| OCS containing             | 119 | 2.33%| 22 | 1.37%| 90 | 2.70%| 7  | 4.32%|
| ICS-LABA containing        | 441 | 8.63%| 193| 12.00%| 248| 7.43%| 0  | 0.00%|
| ICS containing             | 60 | 1.17%| 12 | 0.75%| 48 | 1.44%| 0  | 0.00%|
| LTRA                      | 176 | 3.44%| 53 | 3.30%| 123| 3.68%| 0  | 0.00%|
3.2.2.3 Non-controller Medications Pattern

Of the 12,094 (45.98%) patients who did not receive treatment with any controller medications, 70.16% used relievers or other medications (including antibiotics, Traditional Chinese medicine (TCM), anti-histamine, cough, mucolytic and cough mucolytic combination) during follow-up visits with 60.92% receiving relievers plus other medications and 39.08% receiving relievers prescription only. The most common prescriptions were short-acting xanthine derivatives (22.09%), SABA (12.72%) and short course (≤7 days) use of oral corticosteroids (10.91%) in anti-asthmatic relievers, and antibiotics (29.5%), TCM (26.93%), anti-histamine (23.07%), antitussive (22.44%), and mucolytics (14.52%) in symptomatic medications.

3.3 Asthma Severities

A total of 7,996 (30.4%) patients had continuous care by end of 12-month follow-up. The distributions of asthma severity in each 3-month OWU are presented in Figure 4. The proportion of mild, moderate and severe patients were 76.86%, 17.88% and 5.25%, respectively, in 1\textsuperscript{st} 3-month OWU. The proportions of both moderate and severe asthma patients decreased by about half from 1\textsuperscript{st} 3-month OWU to 2\textsuperscript{nd} 3-month OWU and then remained stable from 2\textsuperscript{nd} to 4\textsuperscript{th} 3-month OWUs.

4. Discussion

To the best of our knowledge, our study is the first cohort study investigating the initial prescription and changes in newly diagnosed asthma patients. Our study represents the clinical practice in China by following a heterogeneous adult and adolescent populations treated in both tertiary and secondary hospitals with a wide regional coverage. The results of our study spotlight real-world management of asthma care and complement previous data from cross-sectional population-based surveys.

Controller medications should be initiated as soon as the diagnosis of asthma is made and ICS-containing medications are the preferred long-term controller [2]. Regular daily combination low dose ICS-LABA as the initial maintenance controller treatment is recommended in moderate and severe asthma [26][27]. More recent data have demonstrated that treatment with budesonide-formoterol solely as-needed prevents exacerbations and loss of lung function in mild asthma, especially for patients who do not adhere to regular ICS therapy [28][29][30]. Previously, a prospective observational study comprising 45 tertiary hospitals showed that over 90% of newly diagnosed patients were initially prescribed ICS-LABA from respiratory specialists, which represented the best practice [31]. In our study, fewer than half of the patients received any controller medications and only about 14% patients received ICS-containing prescriptions initially. In addition, a disproportionately higher percentage of controlled prescriptions were dispensed in tertiary hospitals. This evidence highlighted major variation in asthma treatment among hospitals of different tiers and specialties which might lead to the unsatisfied level of asthma control.
LTRA may be appropriate for initial controller treatment for some patients who are unable or unwilling to use ICS or with concomitant allergic rhinitis (AR) [32][33]. A national cross-sectional study indicated that 26.7% of asthma patients had AR [1] and a meta-analysis showed that the prevalence of asthma with AR in China was as high as 38.97% [34]. In our study, approximately 18% of the patients were prescribed with LTRA initially and more than half LTRA prescriptions were combined with other controller medications, which could be explained by presence of AR in newly diagnosed asthma patients.

Oral corticosteroids (OCS) are used to manage asthma exacerbations and severe, uncontrolled asthma. OCS prescribing was common in US and western Europe countries that 14–65% asthma patients were OCS users and annual prevalence of high dosage OCS use remained stable at ~3% to 7.6% [35][36]. In this study, we found that OCS use as controller varied from 2.09% to 9.76% over the study period and the proportions of OCS use were nearly two times frequent in secondary hospitals comparing to tertiary hospitals. The data might provide important clinical insights to inform primary care physicians and specialists involved in the management of severe, uncontrolled asthma.

GINA no longer recommends treatment of asthma in adults and adolescents with SABA alone for safety concerns [37]. While the use of as needed SABA provides rapid relief of asthma symptoms, it does not address the underlying inflammatory process and does not protect patients from exacerbations [38]. Recent data showed that overuse of SABA in asthma was associated with increased risk of exacerbation and mortality and one-third of asthma patients were SABA over users (three or more canisters per year), of whom 28% had not been treated with anti-inflammatory drugs [39]. In our study, 16.57% patients received SABA alone or in combination with other non-controller prescriptions initially, and among the 45.98% (12,094) patients over follow-up period without controller treatment, 12.72% patients received SABA. In addition, our study shows that other anti-asthmatic relievers like SAMA, SABA/SAMA combination, short-acting xanthine derivatives, short course use of corticosteroids were prescribed in over 80% patients from the 12,094 pool during follow-up period. Asthma patients mostly experienced asthmatic associated signs or symptoms like cough, constriction in the chest and throat, sneezing, nasal discharge, pharynx itching before or during asthma exacerbations [40]. Our study also indicated that medications dispensed for treating symptoms/conditions likely associated with asthma were common, including Traditional Chinese medicine, anti-histamine, antitussives, mucolytics, etc. These symptomatic medications were probably overused like SABA, and whether might associate with increased risk of exacerbation.

It was noticed that approximately 30% percentage patients received antibiotics during follow-up period which might be not rational. Indeed, there is very limited evidence that antibiotics may help people having asthma attacks [41].

For asthma care, GINA provides specific recommendations for choices of pharmacotherapy and need of regular clinical follow-ups for monitoring of asthma control and adjusting therapy as appropriate. Poor adherence is common in patients with asthma and is often associated with increased health care resource use, morbidity, and mortality, including Chinese asthmatics [42][43]. In our study, only about 30% of the patients had uninterrupted clinical visits ensuing initial asthma diagnosis by end of 1 year follow-up. And lack of continuum of clinical encounters was most notable during the first 6 months following the diagnosis for patients treated in both tertiary and secondary hospitals. Moreover, the prescriptions of controller slightly increased at first 3 months after initial treatment but decreased notably from 6th months onward in follow-up period. And controller medications tended to discontinue in patients with mild-moderate asthma. While the reasons for lack of continuity of care and discontinuation of controller prescriptions are beyond the scope of present study, likely they are associated with asthma control or symptom relief, medication beliefs, treatment adherence, out of pocket cost, etc [44].

Only a small proportion, less than 3%, of patients in our study were treated in primary hospitals. At initial diagnosis, compared to patients treated in tertiary or secondary hospitals, patients treated in primary hospitals received more
OCS, theophylline and other controller treatment and more frequent use of relivers and symptomatic medications. Interestingly, a greater proportion of these patients had subsequent continuity of hospital visits relative to patients treated at higher tiered hospitals.

In health service research, asthma severity is commonly assessed retrospectively based on prescription of treatment steps [2] and changes of prescriptions at the follow-up visits are likely to be indicative of worsening or improvement of underlying asthma severity [45][46][47]. We applied the same methodology in characterizing asthma severity at each three-month observation period in patients with at least 12-month follow-ups. Previously, a cross-sectional study of asthma showed that, in 2,034 diagnosed asthmatics, 6.00% were considered as severe cases [48], but the investigators used somewhat different criteria in determining asthma severity; patients were only considered having severe asthma if they had achieved asthma control with two or more controllers (step 4) for over 6 months [49]. In another cross-sectional survey, 75.31% of 1,191 self-reported respondents was deemed to have mild asthma based on prescribed medications [50]. Our data showed that about one quarter of patients had moderate or severe asthma during the first 3 months after the diagnosis and then decreased by half by 6 months and plateaued for the remaining follow-up period. The patient profile with regarding to disease severity appeared to be representative of general asthma population.

The national cross-sectional China Pulmonary Health (CPH) study has shown that only 10·2% diagnosed asthma patients received therapy with ICS and primary care services should be improved especially in rural and remote regions [1]. In our study, we found that greater than 70% asthma patients were diagnosed in the departments other than respiratory and this was more so in secondary hospitals. Even for patients in urban areas, both ICS and other controller medications were underused initially and tended to be discontinued in spite of patient adherence to follow-up visits. Symptom ‘remission’ or patient in ‘mild’ asthma could be the reasons. On the other hand, a large proportion of patients received relief drugs including anti-asthmatic relievers and symptomatic medications over follow-up period, which indicated that, for patient with worsening asthmatic or atypical symptoms, most physicians tended to use symptom relief drugs and were less likely to increase use of controller medications. This symptomatic treatment was probably attributable to underestimated patient assessment of asthma control. In addition, patients may have difficulties making an appointment with respiratory specialists, especially in lower tiered hospitals, in which patients tend to receive less optimal care for asthma treatment.

As a retrospective study, our study has several limitations. First, our study was based on data extracted from an existing database, which was over represented in secondary hospitals in urban areas, which could bias the anti-asthmatic medication usage toward more affluent regions and, as such, findings from our study mostly reflected the urban asthma population. Secondly, by design, our study only included individuals who had actively engaged with their health care providers. Lack of follow-up visits following the initial asthma diagnosis could be explained by discontinuation of asthma care, limited follow-up period recorded in the database, or loss to follow-up due to other reasons, e.g. relocation. Given the relatively low mobility of Chinese population, we believe that lack of follow-up visits was mostly due to discontinuation of asthma treatment. Our analysis only included individuals who had been in regular contact with the health care system for ailments other than asthma before the index date. By doing so, we may have minimized the lost to follow-up due to other reasons, e.g. health insurance coverage. Finally, the severity of asthma was determined by using the asthma medications as a proxy measure and this methodology is premised on physician's adherence to current practice guidelines [51]. When asthma treatment is deviated from the guidelines, asthma severity estimate would have errors or bias with an undefined imprecision [52].

5. Conclusions
In newly diagnosed asthma patients, ICS-containing treatment and other controller medications were significantly underused while symptom-relief drugs including anti-asthmatic relievers and symptomatic medications, on the other hand, appeared to be overused. Poor adherence to current guidelines were common and more noticeable in lower tiered hospitals. These findings call for needs of more aggressive asthma management and more educational efforts in China.

**Abbreviations**

AR: allergic rhinitis  
GINA: The Global Initiative for Asthma  
ICS: inhaled corticosteroid  
ICS-LABA: Inhaled corticosteroid and long-acting β2-agonist combination  
LAMA: long-acting muscarinic antagonist  
LTRA: leukotriene receptor antagonist  
MCS: mast cell stabilizer  
OCS: oral corticosteroid  
OWU: Observation Window Unit  
SABA: short-acting β2-agonist  
SAMA: short-acting muscarinic antagonist  
TCM: Traditional Chinese medicine

**Declarations**

- **Ethics approval and consent to participate:** Not applicable  
This is a retrospective analysis from a structured electronic hospital medical record system constructed and based on ambulatory and hospitalization encounters with de-identified patient level data, and not involving human participants, human data or human tissue  
- **Consent for publication:** Not applicable  
This manuscript does Not contains any individual person's data in any form (including individual details, images or videos), consent to publish.  
- **Availability of data and material**  
We wish to share the raw data and please find the file named as 'Raw data.xlsx'  
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- **Competing interests**

The authors declare that they have no competing interests.

- **Authors’ contributions**

ZH, SC, JX and YG were involved in the conception and design of the study, the acquisition of data, and the data analysis and interpretation. XH, HZ, HD, CY and XL were involved in the data analysis and interpretation. All authors contributed to drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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**Figures**

**Figure 4. Distribution of Severity in Each 3-month OWU (N=7996)**

Note:
1. OWU: Observation Window Unit. 1 OWU= 3 months
2. Asthma severity classification was based on the last prescription of controller medication according to GINA2018.
3. 1-month grace period before and after the OWU was permitted to account for patients’ early or late visit.

**Figure 4**

Distribution of Severity in Each 3-month OWU