國立臺灣大學電機資訊學院生醫電子與資訊學研究所

博士論文

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Doctoral Dissertation

臨床療效及安全性之主動監測系統

Active Surveillance System for Clinical Effectiveness and Safety

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國立臺灣大學博士學位論文
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臨床療效及安全性之主動監測系統

Active Surveillance System for Clinical Effectiveness and Safety

本論文係林峰祺君（學號 D02945017）在國立臺灣大學生醫電子與資訊學研究所完成之博士學位論文，於民國 108 年 1 月 16 日承下列考試委員審查通過及口試及格，特此證明

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中文摘要

儘管隨機對照試驗被認為是新藥批准的標準研究方法，但仍無法檢測到所有不良藥物事件。由於許多嚴重的藥物不良反應，許多藥物在市場批准後仍被撤回。因此，藥品核可後，病人的藥品使用安全性和有效性的持續性監測和評估是非常重要的。

為了了解病人群對藥品使用安全性、有效性、即時性與持續性監測，並提供臨床效果研究資料的取得與應用。我們開發了基於網路服務的臨床安全監測系統，此系統基於台大醫院的醫療整合資料庫，實作了一系列的以電子病歷資料的擷取自動化流程，方便醫療研究人員在系統介面設計自己的研究參數，指定藥品安全監測分析方法，進而透過此平台產生監測之報告。為了驗證系統的結果，我們在該研究中建立了兩個臨床應用。我們研究了骨質疏鬆性骨折患者的醫療指引的順從性。 第二個應用我們調查了 NOACs 和 warfarin 在非瓣膜性心房顫動患者中的有效性和安全性的差異。

根據醫療指引我們透過系統檢索了 2010 至 2014 年間，識別出 2,193 新罹患骨質疏鬆性骨折的病人，藉由系統的進一步的篩選功能，共找出了 1,808 位病人 (82.44%, 1,808/2,193)在三個月內有回到臺大醫院繼續接受治療，其中僅有 464 位病人 (21.16%, 464/2,193) 在一年內有根據醫療指引服用抗骨質疏鬆的藥物。

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我們在 2010 年至 2015 年期間識別出 2,357 名的病患，為新使用口服抗凝劑的非瓣膜性房顫患者，並進一步分析了缺血性中風作為臨床療效的比較與顱內出血作為安全性的比較。在缺血性中風的結果中，與服用 warfarin 病患相比，NOACs用戶在調整意向治療（ITT）分析中，罹患缺血性中風的風險顯著降低（P = 0.01）。在治療（AT）分析中具有風險則沒有差異（P = 0.12）。 在顱內出血安全性比較，NOACs 病患在 ITT 分析為（P = 0.68）和 AT 分析為（P = 0.15）其風險並沒有差異。

由此可知，臨床安全監測系統提供了可參數化的設計，研究人員可以專注於解決臨床研究問題，此系統則可以進行資料自動擷取，並進一步產生監測報告。此系統可以加速臨床研究的流程，並提供決策者基於電子病歷的證據，以協助醫院或醫事人員進行決策。

關鍵字：臨床監測系統，骨質疏鬆性骨折，藥品安全，抗凝血劑

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ABSTRACT

Although the randomized control trial is considered as a gold standard research approach for the new drug approval, such a trial may fail to detect all the adverse drug events. Numerous drugs were still withdrawn after the market approval because of the unexpected severe adverse drug reaction. Therefore, it is a critical issue to establish a well-design effective and convenient active post-marketing drug surveillance system, which is the process of continuous monitoring and evaluation of the drug safety and effectiveness after their listing.

We implemented a web-based clinical surveillance system, the National Taiwan University Hospital Clinical Surveillance System (NCSS) that can integrate the workflow of cohort identification to accelerate the survey process of disease and medication prescription patterns and provide a high reusability infrastructure for a computerized workflow to capture relevant longitudinal clinical data and make those data repositories reusable.

In order to valid the result of NCSS, we established two clinical applications in the study. The first application of the NCSS, we looked at the identification of osteoporotic fracture patients and their utilization in pharmacological therapy. The second application, we investigated the difference of effectiveness and safety between NOACs and warfarin in the patients with non-valvular atrial fibrillation.

By applying the NCSS, we efficiently identified 2,193 patients who were newly diagnosed with a hip or vertebral fracture between 2010 and 2014 at NTUH. By adopting the filter function, we identified 1808 (82.44%, 1808/2,193) patients who continued their

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follow-up at NTUH, and 464 (21.16%, 464/2,193) patients who have prescribed anti-osteoporosis medications (AOMs), within 3 and 12 months post the index date of their fracture, respectively. On average, only 35% of female and 28% of male osteoporotic fracture patients initiated AOM therapy to prevent a subsequent fracture. More effort is warranted to improve the quality of care with these patients.

We demonstrated the practical example of investigating the difference of effectiveness and safety between NOACs and warfarin in the patients with non-valvular atrial fibrillation at NCSS. We efficiently identified 2,357 non-valvular AF patients with newly prescribed oral anticoagulant between 2010 and 2015 and further developed one main cohort and two sub-cohorts for measuring ischemic stroke as clinical effectiveness outcome and intracranial hemorrhage as safety outcome separately. In ischemic stroke, compared to warfarin users, NOACs users have a significantly lower risk of ischemic stroke after adjusting for age, sex, comorbidity and co-medication in intention-to-treat (ITT) analysis (P = 0.01) but have a comparable risk in as-treated (AT) analysis (P = 0.12) after the 2-year follow-up. In intracranial hemorrhage, NOACs users have a comparable risk of ICH both in ITT (P = 0.68) and AT analysis (P = 0.15).

The NCSS systems can integrate the workflow of cohort identification to accelerate the survey process of clinically relevant problems and provide decision support in the daily practice of clinical physicians, thereby making the benefit of evidence-based medicine a reality.

Keywords: Clinical Surveillance System, Osteoporotic Fractures, Pharmacovigilance, Drug Safety, Anticoagulants

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Chapter 1. Introduction

1.1 Background and Significance

Approval of a new drug has to undergo at least two-phase randomized control clinical trial included hundreds or thousands patients to prove both its efficacy and safety, in comparison to placebo or to a recognized current treatment. Although randomized control trials are considered the gold standard for approval of new drugs, these trials may be ineffective in detecting all adverse drug events in "real-world" clinical practice. Numerous drugs were withdrawn after market approval due to unexpected severe adverse drug events [1]. Many studies have indicated that the relatively small sample size of the clinical trials compared with target patients in the real world is the major barrier to detecting very rare but serious or even fatal adverse events [2-4]. Moreover, such trials typically employ stringent inclusion and exclusion criteria that may exclude a substantial portion of the broader population of target patients, especially the older people, and may limit the generalizability both of the efficacy and safety finding. Therefore, it is critical to establish a well-designed, effective, and efficient active post-marketing drug surveillance system to continuously monitor and evaluate drug safety and effectiveness after a drug is launched.

Clinical surveillance provides information on disease prognosis and post-marketing medication safety, which helps researchers identify potential clinical issues [5, 6]. Traditional clinical surveillance relied on the results from clinical trials, and observational studies of administrative databases. However, these studies not only require a lot of valuable resources but also face a very long time lag. Abundant studies [7-11] have been describing the difficulty of reducing gaps between clinical research needs and proper data management technique.

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Therefore, how to develop an automated system with the capability to use routinely collected electronic healthcare data to support clinical surveillance is an important issue.

For clinical practitioners or researchers, how to reduce gaps between evidence and practice in a rapid and efficient manner is still an unresolved problem. The review of different scenarios to interpret clinical issues is often very complex and time-consuming. Therefore, how to develop an automated system with the capability to use routinely collected electronic healthcare data to support clinical decisions is an important issue. Technical gaps hinder the feasibility of conducting clinical research, and delay the application of research results that would otherwise improve clinical practice. Synthesizing different perspectives to enhance the quality of healthcare has continued to be a significant driving factor for the development of the informatics system.

Nonetheless, only a few successful efforts for high reusability and computerized workflow infrastructure been accomplished in Taiwan to date. Therefore, we decided to implement a web-based clinical surveillance system extensible to interdisciplinary collaboration and data sharing.

1.2 Clinical Surveillance Program

In 2015, the National Taiwan University Hospital (NTUH) launched a new 3-year strategic plan to build an active pharmacovigilance platform. We implemented a web-based clinical surveillance system, the National Taiwan University Hospital Clinical Surveillance System (NCSS), to leverage developments in information technology to support the clinical needs of quality medical assurance and clinical research.

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According to the definition of the World Health Organization (WHO), pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem [12]. In recent years, due to the vigorous development of the large-scale database, a large number of samples and the advantages of individual diversity, pharmacovigilance has developed the idea of active monitoring [13]. Therefore, the advantage of a hospital database is that it reflects the real-world patient medication situation and drug safety assessment, and tracked for several years.

In addition, the hospital database has abundant and immediate patient medical information that including self-paying drugs, lab data, and disease diagnosis all contribute to the timely analysis of the essential nature of the user, the type of prescription, and the safety and effectiveness of the follow-up drugs after the new drug approved by the hospital. The immediate information on these new drugs is not available in the commonly used national health insurance database of Taiwan, which can have up to 3 years of time lag. Therefore, the NTUH launched a new 3-year strategic plan to develop a computerized system to integrate the workflow of cohort identification to accelerate the survey process of disease and medication prescription patterns. By using a standard query interface to reduce the labor and time spent on data collection, combined with server-side and batch process, it provides automated extraction of data for researchers for analysis.

1.3 Two Clinical Applications of the NCSS

In order to valid the result of NCSS, we established two clinical applications in the study. The first example of a clinical application of the NCSS, we looked at the identification of osteoporotic fracture patients and their utilization in pharmacological therapy. Osteoporotic fractures, a major consequence of osteoporosis, are associated with a high mortality rate,

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increased risk of re-fracture, and poor quality of life, and incur heavy society and economic burden.

According to a report from the Global Burden of Disease Study project, the global burden of osteoporosis-related problems has doubled in the past two decades and has shown a continuous increase in recent years. In 2016, 441,230 documented deaths could be attributed to osteoporosis-related problems [14, 15].

In the United States, the direct economic burden of osteoporotic fractures was approximate $17 billion USD in 2005, and is projected to increase 50% by 2025 [16]. Fortunately, the safety and efficacy of anti-osteoporosis medications (AOMs) used by patients with established osteoporotic fractures have been ascertained [17-21]. However, despite the readily available and effective treatment for osteoporosis, a care gap between established osteoporotic fractures and the pharmacological prevention of subsequent fractures is still being discussed worldwide [22-25]. We aimed to identify the unmet treatment needs for patients encountering major osteoporotic fractures with the NTUH based clinical surveillance system.

The second application we aimed at identifying patients who take the medication for NOACs at NCSS and compared with warfarin for utilization and clinical outcomes. Atrial fibrillation (AF) is an irregular and often rapid heart rate that can increase your risk of stroke, heart failure and other heart-related complications. AF is the most common form of arrhythmia. About 2% of adults in white people have AF and about 1% of adults in Asian countries. The overall prevalence is higher in developed countries than in developing countries.

A global large-scale statistic shows that in 2010, the number of global AF patients was about 33.5 million, of which men accounted for 20.9 million, and women accounted for 12.6

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million. The prevalence rate increased with age, but the result may be under-estimated. This is because the AF with mild symptoms is not easily diagnosed [26, 27].

Many innovative advances have emerged for the diagnosis and management of AF, including a new scoring system for the prediction of stroke and bleeding events, and non-vitamin K antagonist oral anticoagulants [26, 28]. Vitamin K antagonists (VKA) such as warfarin, have been the only oral anticoagulation agent available for stroke prevention for decades [29]. Warfarin treats and prevents blood clots by decreasing the production of several clotting proteins that rely on vitamin K. However, because of the variations in doses needed for each patient, warfarin requires frequent laboratory monitoring and dose adjustment to maintain blood levels within the target range.

In recent years, the approval of NOACs (i.e., dabigatran, rivaroxaben, and apixaban) is a breakthrough treatment in preventing ischemic stroke among AF patients and have been introduced as alternatives therapy for warfarin. Compared to warfarin, all these NOACs demonstrated similar or better stroke prevention and similar or lower risks for bleeding in the clinical trials. Moreover, NOACs have fewer drug-food or drug-drug interaction and do not require regular monitoring. Although the effectiveness and safety of NOACs have been proven by clinical trial, whether the outcomes observed in the clinical trial are also reflected in the real world clinical practice is still being discussed worldwide. We aimed to investigate the difference of effectiveness and safety between NOACs and warfarin in the patients with non-valvular AF with the NTUH based clinical surveillance system.

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1.4 The Aim of this Study

In summary, the goal of the study is to develop the technical/scientific operations for scientists to evaluate safety questions more rapidly than traditional methods. Using electronic medical database, scientists can obtain responses to their safety concern in days instead of months. However, the clinician/scientist need to have technical experience with the electronic medical database in order to have such a fast turnaround. Not all scientists have the informatics training technical experience. Therefore, this study aims to design a thin client architecture, which allows the researchers to focus on the design of research though setting parameters on the web page on the client side. The complex and large computing delegate will be done on the server side. As a result, the researchers do not need to have any technical knowledge or own a high performance computer for the data analysis.

Our efforts will be based on two highly diffusible, highly reusable and thin client architectures for research network. The platform provides a high reusability infrastructure for a computerized workflow that captures relevant longitudinal clinical data and makes those data repositories reusable. Finally, the platform has been used for multi-municipality surveillance.

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Chapter 2. Literature Review

2.1 Introduction to Clinical Drug Surveillance System

Drug surveillance can be classified as passive or active, depending on the way the data is collected. A passive post-marketing drug surveillance systems [30] relies on voluntary reports or the collection of spontaneously reported adverse events from healthcare providers. These are limited by incomplete information in the reports, often fails to report events with well-established causality, diminishing the ability to establish the prevalence. In contrast, an active surveillance system applies healthcare records to determine adverse events associated between drugs and adverse events. Further studies [31, 32] are ongoing interest in developing systems that can incorporate and use existing electronic data such as administrative claims and electronic health record databases to enable active surveillance for ADEs.

The growing interest in using EMRs databases for drug safety surveillance has spurred development of new methodologies for signal detection [33]. Previous studies [32, 34] have shown that the timely detection of safety signals remains a challenge, and there has been a shift towards utilizing linked electronic healthcare databases for active drug safety surveillance [35-37]. Characterization of safety signals relies on the observation and systematic monitoring of their effects in “real world” practice. The databases can reflect the real-world patient medication situation and drug safety assessment, and it can facilitate earlier detection of potential safety issues. Thus, proper evaluation of signal detection methodologies calls for the creation of a reference standard. It can arise the awareness about potential adverse drug reactions to what this type of surveillance can add to existing systems and whether these database platforms have enough power to detect safety signals adequately.

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According to Aronson et al. [38] define the concept of an active surveillance system in epidemiology has the following features:

1. It is designed for post-marketing surveillance of pharmaceutical products.

2. It has a goal of generating post-marketing drug safety information.

3. It does not require personnel to initiate safety reports (describing individual cases).

4. It uses real-world data that are generated from routine practice, requiring no direct patient contact.

In Asia, the Shanghai Drug Monitoring and Evaluative System (SDMES) is an evaluation and surveillance system designed to understand a drug's full profile in the post-marketing environment [39]. They denote that evaluating signals generated from the ADR reporting system was difficult because it only represents a fraction of the actual adverse drug-related events. To resolve this problem, they consisted of three different databases including a health survey database, a hospital medical records database and the spontaneous ADR reporting database. The system can longitudinally track a patient by record linkage using patient identification cards or Medicare numbers. However, there are limitations to these data. The data for each individual were collected only once and cannot automatically update to the database.

There is the Asian Pharmaco-epidemiology Network (AsPEN) [40, 41] which was formed to provide a mechanism to support the conduct of pharmaco-epidemiological research and to facilitate the prompt identification and validation of emerging safety issues among the Asian countries. They employed the prescription sequence symmetry analysis (PSSA) for signal

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detection. The strengths of PSSA characterized with case-only based and least requirement in data privacy. The PSSA can be validated by testing the association case and control groups and visualized temporarily between index and outcome medication, however, PSSA may be affected by prescribing or event trend over time such that possibly leads to a biased effect estimate. Therefore, they employed a null-effect sequence ratio to reduce for the underlying utilization patterns of drug outcomes potential bias when the trends of prescribing pattern are stable in PSSA analysis.

In European, the European Medicines Agency developed a project, EU-ADR, which implemented a computerized system to detect ADEs with exploiting clinical data from electronic healthcare records of over 30 million patients from several European countries [42]. A distributed network approach that requires standardization of data model from the different databases, so they developed a data managing software called Jerboa. The Jerboa can query patient-level data in the different databases and aggregate de-identified data to a central repository for evaluation. They described the advantage of multiple, routinely collected, aggregated healthcare data for large scale drug safety monitoring. The EU-ADR provided the summary of drug utilization about background incidence rate of events, incidence rates during drug use and patterns of drug use. We think that combine EU-ADR and spontaneous reporting system would strengthen current signal detection activities. However, in pharmacovigilance practice, the process of signal detection is a hypothesis, and additional clinical evaluation is necessary to verify a causality relationship between the signal and the event [43, 44]. At the current stage, the EU-ADR is a centralized integrated database, and there cannot provide further analysis, such as minimize the confounding effects or calculate the hazards ratio.

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Table 1. Literature summary on Electronic Clinical Surveillance

Author	Initial Year	Main Concept	Geographic Coverage
Du, W., et al. [39]	2007	A drug's full profile in the post-marketing environment	China
AsPEN collaborators [40, 41]	2013	Using prescription sequence symmetry analysis (PSSA) for signal detection	Asia
Brown, J., et al. [45, 46]	2008	Data harmonization and develop the Propensity Score Matching Tool	National
Coloma, P.M., et al. [42]	2011	A large-scale drug safety monitoring	International
Obeid, J. S, et al. [11]	2013	Reusable tools for project-specific clinical and translational research data	International
Natter, M.D., et al. [10]	2013	A self-scaling, interoperable platform for collaborative data sharing	National
Lowe, H.J., et al. [48]	2014	An anonymous patient cohort discovery tool and data management solution	National
Waitman, L.R., et al. [7] Fleurence, R.L., et al. [8]	2014	An analyzable research database that enhanced the performance of a cross-networking query	National

In the USA, the Food and Drug Administration (FDA) launched the Sentinel Initiative for the establishment of a national electronic monitoring system for medical product safety in 2008 [45, 46]. Until 2016, they disclosed the completion of the Mini−Sentinel pilot and the transition

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to the full Sentinel System. Through the Sentinel Common Data Model and automated analytical tools, the FDA can rapidly query and monitor information from the insurance claims data [47]. In addition, the PCORnet [7, 8] developed a common data model derived from the Sentinel to support the development of an analyzable research database that enhanced the performance of a cross-networking query. To consider the system architecture and data management structures, the Research Electronic Data Capture (REDCap) [11] developed reusable tools for project-specific clinical and translational research data. We found that the design of the Translational Research Integrated Database Environment (STRIDE) [48] for an anonymous patient cohort discovery tool provides a flexible research data management solution. Furthermore, the Integrating Biology & the Bedside (i2b2) [10] proposed a self-scaling, interoperable platform for collaborative data sharing. We summarized the literature into the challenges of active clinical surveillance, shown as Table 1.

2.2 The Propensity Score Matching

There is a growing interest in using observational or nonrandomized studies to estimate the safety and effectiveness of drugs on outcome research. In a randomized experiment, the randomization enables unbiased estimation of treatment effects and control groups with approximate balance on background measurements such as age, gender and medical history [49]. However, the case selection is often influenced by subject characteristics in observational studies or nonrandomized studies [50]. For example, if the subject is considered risky for older patients and patients assigned to the control group may be older than the active treatment group. A risk comparison of observed study in these active treatment and control groups would lead to a biased estimate of the treatment effect because of the imbalance in age. In order to generate unbiased treatment effect estimates using observational data, patients should be sub-classified

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or matched such that case and control patients within a match are well balanced on crucial observed covariates.

The propensity score was defined by Rosenbaum, P.R. and D.B. Rubin [51]. The propensity score is the probability of treatment assignment conditional on observed baseline characteristics that its applications include:

1. It matched sampling on the univariate propensity score, which is a generalization of discriminant matching.

2. The multivariate adjustment by sub-classification on the propensity score where the same subclasses are used to estimate treatment effects for all outcome variables and in all subpopulations

3. The visual representation of multivariate covariance adjustment by a two-dimensional plot.

The true propensity score is not known in an observational study, so we must estimate using the study data. An important concept of any propensity score analysis is assessing whether the distribution of measured baseline covariates is similar between treated and untreated subjects with the same estimated propensity score. Using propensity score matching approach, matched sets of treated and untreated subjects with similar probability of the propensity score are formed. Inferences about treatment effect made using this approach are valid only if, in the matched sample, treated and untreated subjects have similar distributions of measured baseline covariates.

Comparing the similarity of treated and untreated subjects in the matched sample should start with an examination of the means or medians of continuous covariates and the distribution of their categorical counterparts between treated and untreated subjects. The standardized

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difference can be used to compare the mean of continuous and binary variables between treatment groups [52]. For continuous variables, the standardized difference is defined as

$$d = \frac{(\bar{x}_{treatment} - \bar{x}_{control})}{\sqrt{\frac{s^2_{treatment} + s^2_{control}}{2}}},$$

where $\bar{x}_{treatment}$ and $\bar{x}_{control}$ denote the sample mean of the covariate in treated and untreated subjects, respectively, while $s^2_{treatment}$ and $s^2_{control}$ denote the sample variance the covariate in treated and untreated subjects, respectively. For dichotomous variables, the standardized difference is defined as

$$d = \frac{(\hat{p}_{treatment} - \hat{p}_{control})}{\sqrt{\frac{\hat{p}_{treatment}(1-\hat{p}_{treatment}) + \hat{p}_{control}(1-\hat{p}_{control})}{2}}},$$

where $\hat{p}_{treatment}$ and $\hat{p}_{control}$ denote the prevalence or mean of the dichotomous variable in treated and untreated subjects, respectively. The standardized difference is not influenced by sample size, so it can be used to compare balance in measured variables between treated and untreated subjects in the matched sample with that in the unmatched sample.

By comparing patients with similar estimated propensity scores, we can design an observational study that mirroring the separation of study design and outcome analysis in randomized experiments.

2.3 Survival Analysis

Outcomes research concerns about understand the end results of particular health care practices and interventions, there is a need for a scientific discipline to bridge the capabilities

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of the medical profession and the best interests of patients and society. The outcome includes effects that people experience and care about, such as a change in the ability to function. The primary event of interest in those studies is a relapse, adverse drug reaction and death or development of a new disease. The follow-up time for the study may range from a few months to many years.

Survival analysis is one of the primary statistical methods for outcomes research, for which the outcome variable of interest is time until an event occurs [53]. Such data analysis is essential for many facets of legal proceedings including assessing drug safety, estimating years of life lost, evaluating medical therapies and devices reliability, etc. Survival analysis makes inference about event rates as a function of time, refers to the set of statistical methods used to analyze time-to-event data. The following terms are commonly used in survival analyses [54]:

1. Event: patient occurs a failure, like death, disease occurrence, disease recurrence, recovery, or other experience of interest.

2. Time: duration from the beginning of an observation period to an event, or end of the study, or loss of contact or withdrawal from the study.

3. Censoring: If no event occurs in the subject during the study cohort. Censoring arises when the starting or ending events are not precisely observed, which results when the final endpoint is only known to exceed a particular value. We illustrated the example in Figure 1.

4. Survival function: The probability that a subject survives longer than time.

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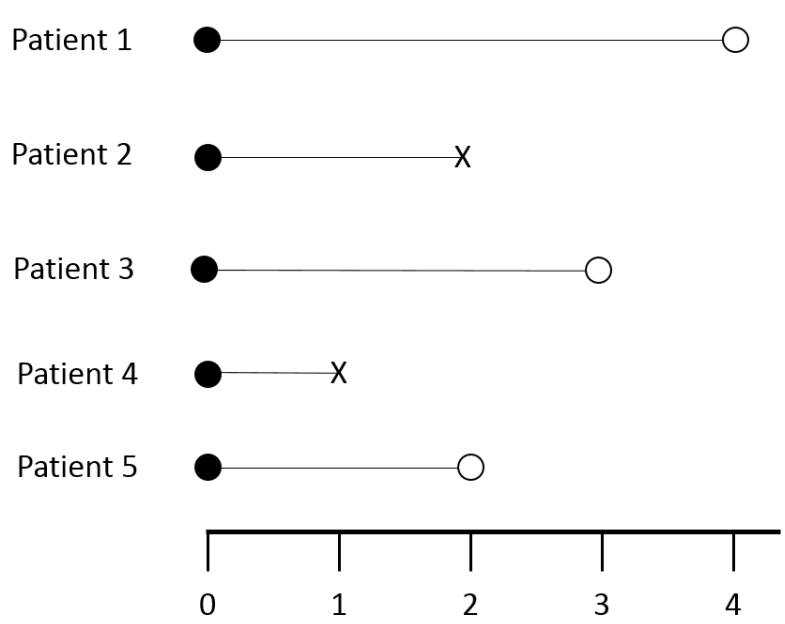

Figure 1. Events and censoring.

In Figure 1 presents this data set in terms of patient time, where each patient is shown as starting at time zero. We know when they started the observation and when the event occurred. The X denotes events and the open circles denote censoring events. In this example, the patient 1, patient 3 and patient 5 were right-censored; for these patients, the last follow-up times are indicated by open circles. The patient 2 and patient 4 were events occurred are indicated by X.

Table 2. The Survival table

Patient No.	Survival Time (Year)	Status
1	4	0
2	2	1
3	3	0
4	1	1
5	2	0

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The data may be represented in tabular form as shown in Table 2. The variable "Survival Time " refers to the time from entry into the observation until an event occurred or loss to follow-up, whichever comes first, and "Status" indicates whether the survival time represents an event (Status = 1) or is censored (Status = 0).

Survival analysis methods depend on the survival distribution, and two key ways of specifying it are the survival function and the hazard function. The survival function is the probability that an individual survives beyond time *t*, formally,

$$S(\mathrm{t}) = \mathrm{P}(T > t), 0 < t < \infty.$$

Let T ≥ 0 be a random variable representing the time to an event of interest. This survival function takes the value 1 at time 0, remains constant over time, and never drops below zero. The survival function usually estimates using the Kaplan-Meier (KM) curve that is an important tool for analyzing censored data but cannot accommodate covariates [55]. The KM estimator is the product over the event times of the conditional probabilities of surviving to the next failure time. Formally,

$$\hat{S}(t) = \prod_{t_i \le t}(1 - \hat{q}_i) = \prod_{t_i \le t}\left(1 - \frac{d_i}{n_i}\right).$$

The example data in Table 3, respectively, the survival time t_i, the number n_i at risk at that time, the number d_i who occur event at that time, the survival probability $q_i = d_i / n_i$, the conditional survival probability 1 - q_i , and the cumulative product, which is the estimate of the survival probability.

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Table 3. Kaplan-Meier estimate

t_i	n_i	d_i	q_i	$1 - q_i$	S_i
1	4	1	0.25	0.75	0.75
2	2	1	0.5	0.5	0.375

For example, the probability 0.75 of being alive at time $t_i = 4$ is the probability 0.75 of being alive at time $t_i = 1$ times the probability 0.375 of being alive at time $t_i = 2$ given that patients are alive at the previous time. There is a censored data between $t_i = 1$ and $t_i = 2$. The final survival probability is 0.375. In survival analysis, censored observations contribute to the total number at risk up to the time that they ceased to be followed. One advantage here is that the length of time that an individual is followed does not have to be equal for everyone. All observations could have different amounts of follow-up time, and the analysis can take that into account [56].

We illustrate the Kaplan-Meier curve using example data in Table 3, as shown in Figure 2. The Kaplan-Meier curve is plotted as a step function, and open and closed circles explicitly show the right-continuity. There is a censored data marked "+" between $S(1)$ and $S(2)$.

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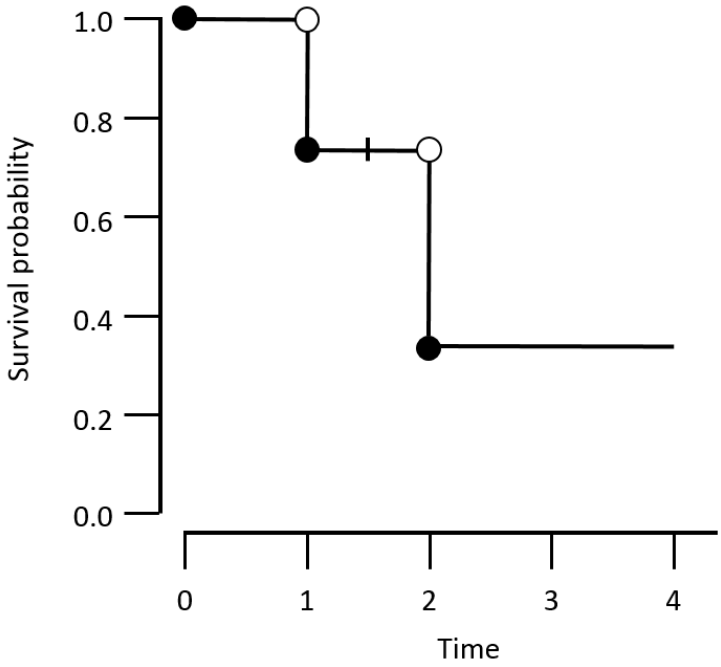

Figure 2. Kaplan-Meier curve

If a study is based on observational data, and the adjustment for confounders is essential. The Cox proportional hazards model has been the most widely employed that is suitable for analyzing the proportional effects of several risk factors on survival [57]. The hazard function can be expressed as:

$$h(t) = h_0(t) \exp(\beta^T X_i).$$

The $h_0(t)$ is the baseline hazard, $Xi = x_1, x_2, \ldots, x_n$ are the covariates, and $\beta^T = \beta_1, \beta_2, \ldots, \beta_n$ are regression coefficients that express the relationship between the covariates and the time to event. Suppose the covariate (risk factor) is dichotomous and is coded 1 if present and 0 if absent. Then the quantity $\exp(\beta^T)$ can be interpreted as the instantaneous relative risk of an event, at any time, for an individual with the risk factor present compared with an individual with the risk factor absent, given both individuals are the same on all other covariates. Suppose the covariate is continuous, then the quantity $\exp(\beta^T)$ is the instantaneous relative risk of an

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event, at any time, for an individual with an increase of 1 in the value of the covariate compared with another individual, given both individuals are the same on all other covariates.

By dividing both sides of the above equation by $h_0(t)$ and taking logarithms, we obtain:

$$\ln\left(\frac{\mathrm{H}(t)}{\mathrm{H}_0(t)}\right) = \beta^T X_i.$$

We call $\mathrm{H}(t)$ / $\mathrm{H}_0(t)$ the hazard ratio. In practice, interest lies in the associations between each of the risk factors or predictors X_i and the outcome. The coefficients β^T are estimated by Cox regression, and represent the change in the expected log of the hazard ratio relative to a one unit change in X_i, holding all other predictors constant. The Cox proportional regression model assumes that the effects of the predictor variables are constant over time. In a Cox proportional regression model, the measure of effect is the hazard rate, which is the risk of failure (i.e., the risk or probability of suffering the event of interest), given that the participant has survived up to a specific time.

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Chapter 3. Clinical Surveillance System

3.1 Data Warehouse

The NCSS integrates a database of electronic medical records at NTUH, which is a medical center in Taiwan with over 2,000 beds. The clinical data models were built using an Oracle 11g relational database, included the demographics, diagnosis, pharmacies, procedures, laboratories, and death records, and were implemented into the data warehouse (DW) process.

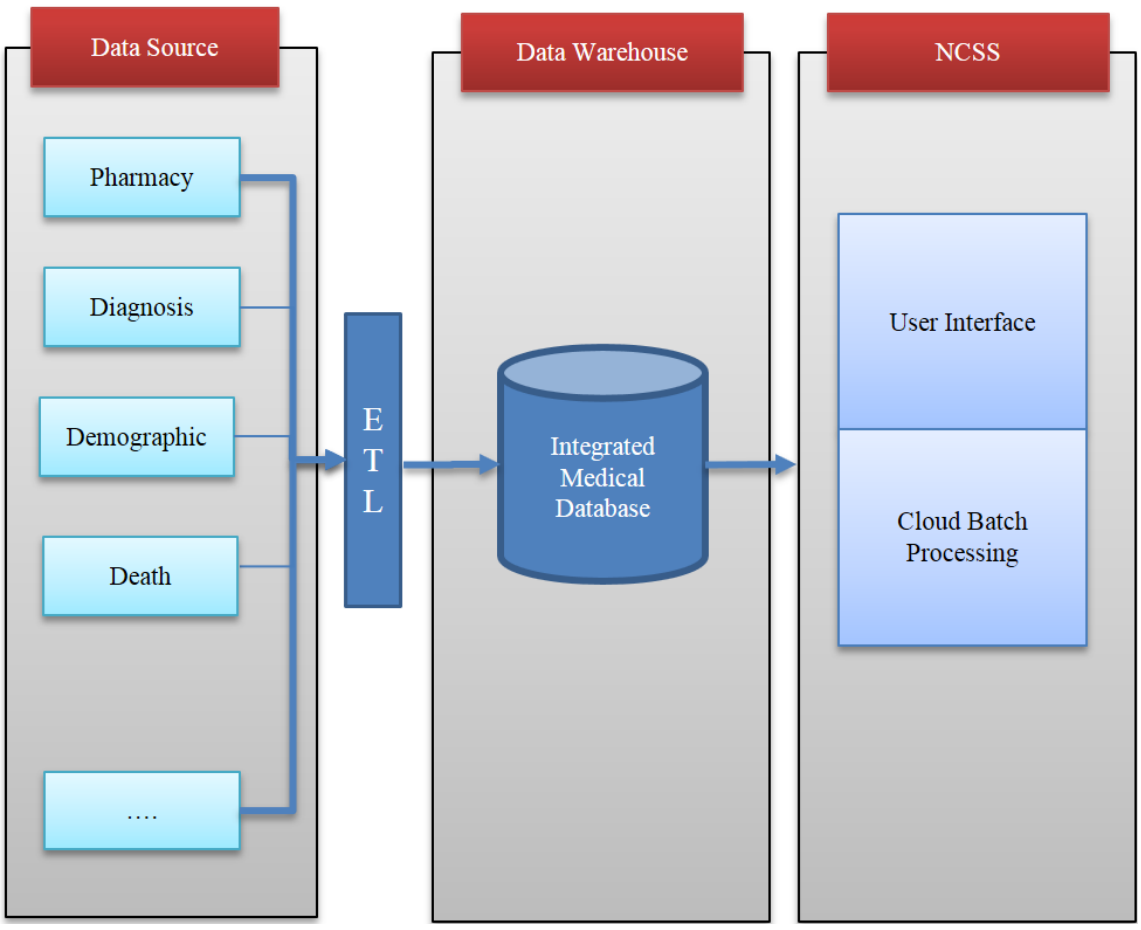

Figure 3. Data warehouse process

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The DW process is the collection of electronic medical records from the Integrated Medical Database (IMDB) through scheduling using an extraction, transformation, and loading (ETL) tool. We integrate clinical data from multiple sources into IMDB. All raw data must do the necessary pre-processing includes: data cleaning, data transformation and reducing data dimensions. We refreshed the database during non-business hours using three steps. First, the system extracted data changes by comparing the time difference with IMDB. Second, personally identifiable information was fully anonymized. Finally, the data is synchronized back to IMDB with a timestamp. This DW provides a data access infrastructure for the NCSS.

3.2 Workflow of NCSS

We aimed to present a web-based NCSS for clinical surveillance in a secure, efficient and interoperable platform. The NCSS using ASP.Net framework (version 4.5, Microsoft) and R statistical environment (www.r-project.org) that designed for web development and cloud batch process. The NCSS configured to run using load balancing, including failover modes, to secure the system's availability and scalability. Firewalls are also installed to enhance the security of the NCSS. In addition, all queries been audited and logged, which assures compliance with Institutional Review Board (IRB) and other regulatory protections for subjects. We designed a thin client architecture that the researchers can focus on the design of research though setting parameters on the web page in client side, and the complex and large computing delegate to cloud batch process in server side. Therefore, the researchers do not need to own a good performance of the computer and lower the computation of big data of barriers. The researcher can aggregate the research report efficiently from the NCSS. The overall workflow of the NCSS is depicted in Figure 4.

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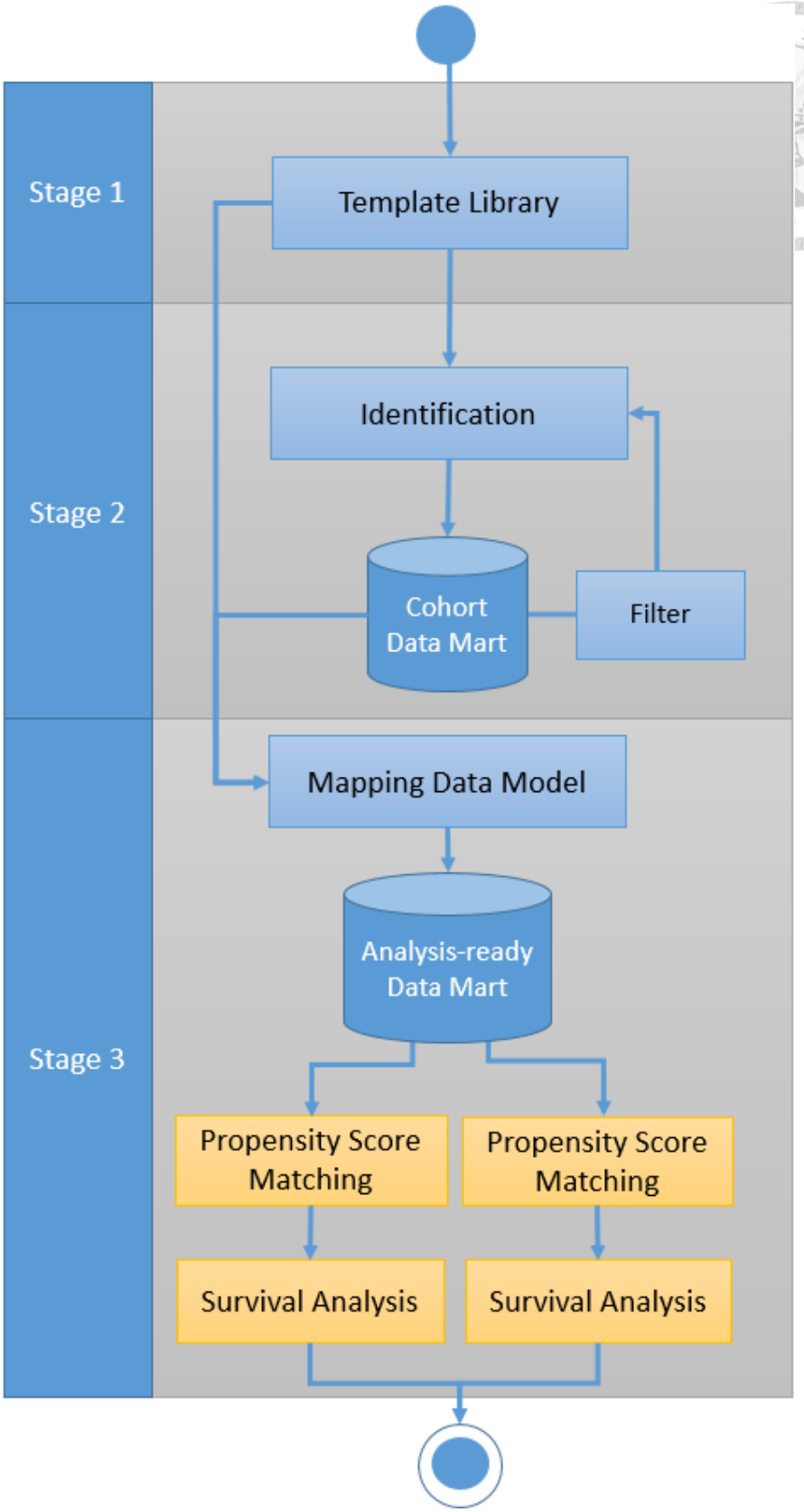

Figure 4. System workflow of NCSS

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3.2.1 Stage 1. Build a Template of Clinical Orders

The process supports the end user, typically a clinical researcher, to predefining a template of clinical orders using a Clinical Orders Navigator in the client side. The researcher can browse and search for different dimensions, such as the diagnosis (ICD-9 or ICD-10), pharmacy (ATC code), procedure and laboratory in the integrated interface. One purpose of the stage is to provide a more flexible and convenient integrated interface that helps the researchers to retrieval related clinical information.

The stage can help clinical researchers build a protocol-based standardized process and save those clinical orders and specific guidelines to the database. The creator of the templates can choose to commit them to Template Library, publicly. All templates submitted to the public Template Library will be reviewed by clinical professionals to ensure quality and accuracy. All researchers can create their own template or use public template applied to the Identification process.

3.2.2 Stage 2. Patient Identification

The stage of Patient Identification, which is the matching of the clinical needs to the optimal cohort study. The stage contains five processes, consisting of identification, REC (Research Institutional Ethics Committee) verification, cloud batch process, data mart of the patient level and Report Service.

(a) Identification: we developed an electronic form to meet the cohort study flow that contains 2 sets as input as follows:

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1. Basic Setting: To define the surveillance topic, and set up the duration of observation from a particular data source, such as outpatient, admission, and emergency. In addition, the setting also supports the selection of specific patient list from Data Mart (patient level).

2. Order Setting: The process supports clinical researchers choose a template as order setting in Clinical Orders Navigator. The clinical orders can be different dimensions, such as the diagnosis, pharmacy, procedure, and laboratory. For example, a disease is defined using several diagnosis codes, such as hip or vertebral fractures, including ICD-9-codes 820, 805, and 806 in Template Library. The researchers can reuse these templates as include/exclude criteria to design their study flow. When researchers finished the electronic form, the system will save those setting to the database and generate a universally unique identifier as case number of this setting.

(b) REC Verification: all setting of Identification needs to be verified by REC. If the setting had been authorized, it would add a task to Task Queue for cloud batch process in server side.

(c) Cloud Batch Process: the cloud batch process maintains a Task Queue. Every task will be executed follow First-In-First-Out (FIFO) mechanism in the batch server that reads the setting of Identification to query eligible patients in IMDB. We adopt the dynamic programming approach to simplify a complicated problem by breaking it down into several simpler sub-problems. The regular period of outpatient visits is about 28 days, so the query divided by month can reduce duplicate records. Given the observation time and divided into sub-queries by each month recursively, we only stored the unique patient ID and first index date. In order to optimize the database query, we set the time of diagnosis, patient ID and clinical orders as a composite index. After completion of the task, the patient list is stored

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into Cohort Data Mart and we send a mail notification to the PI researchers. The batch process also records the cost of each query and the number of patients identified.

(d) Cohort Data Mart (Patient Level): The Data Mart is a collection of the patient list that presents the result of every identification process. The researcher can adopt a patient list from Data Mart as their patient data source to query the next Identification process. Therefore, the Identification process can support a hierarchical structure. This means that the process can generate a new study population based on a previous screening result. The researchers can reuse these patient lists to design cohort study or case control study in fine-grained categorization.

(e) Report Service: the report service contains 3 dashboard view visualize summary statistics for the patient list in Data Mart as the following:

1. View of Characteristics: The view is a demographic summary that helps clarify the characteristics of the patient list. For example, the descriptive statistics of age, gender, body mass index (BMI), income level.

2. View of Longitudinal Incidence Trend: The view presents incidence trend by time series chart and provides a real-time interactive query by time interval, including monthly, quarterly or yearly.

3. View of Source Record: The view presents number of include/exclude patients in every Identification process. If the patient list contains hierarchical structure that runs the process of identification more than once, the Report Service can track all result of identification in the aggregation table.

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3.2.3 Stage 3. Cohort Tree Analysis

The Stage 3 Cohort Tree Analysis contains three processes, Mapping Data Model, Propensity Score Matching, and Survival Analysis.

(a) The Process of Mapping Data Model

Survival analysis studies typically include a wealth of clinical, demographic, and biomarker information on the patients as well as indicators for therapy or other intervention. If researchers want to analyze multiple risk factors, they must do the preprocessing that map each variable to the study population.

We design an automated mechanism that can help the researcher to generate analysis-ready datasets, which combine co-variables and demographic information from the database. First, researchers choose a study population from the Cohort Data Mart, and then define co-variables or search existing template from Template Library. Second, the NCSS receives the request will automatically aggregate analysis-ready dataset and store to the Analysis-Ready Data Mart. Therefore, the analysis-ready data model can be reused again that reduces the computation overhead. Because of this architecture, we can support complicated research situations such as a tree, so we named stage 3 “Cohort Tree Analysis”.

(b) The Process of Propensity Score Matching

A successful outcome analysis should ensure that confounding covariates are balanced between the distinct treatments [50]. The propensity score matching reduces the effects of confounding when using observational data to estimate treatment effects [58]. In this process, the researchers select an analysis-ready dataset from Analysis-Ready Data Mart, and we use

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the logistic regression model to estimate individual propensity scores. Moreover, in strata of subjects that have the same propensity score, the distribution of measured baseline covariates will be the same between treated and untreated subjects. The NCSS uses the nearest neighbor matching [59] with the further restriction that the absolute difference in the propensity scores of matched subjects must be below specified caliper distance. Finally, the NCSS provides the baseline report of the study population including before and after propensity score matching for balancing effect.

(c) The Process of Survival Analysis

In this process, we implemented two different kinds of outcome measurement methods, intention-to-treat (ITT) analysis and as-treated (AT) analysis [60-63]. The ITT analysis states that any subject should be analyzed as if the study population had completely followed the original study design, which means the NCSS would not stop follow-up when the patients who did not fully receive the treatment drug or control drug during the follow-up period. However, AT analysis states that the treatment assignment is based on the actual treatment the patients receive, not the treatment the patients are supposed to receive in origin, which means NCSS would stop follow-up when the patients stop treatment drug or control drug before the occurrence of study event during the follow-up period.

Regarding statistical analysis methods, the NCSS provides two features including Kaplan–Meier Survival Plot and Multivariable Cox Proportional Hazards Model for survival analysis, and visualization functions implemented via server-side R scripts using the “survival” package [64] and the “ggplot2” package [65]. The Kaplan–Meier Survival Plot is one of the ways to measure the survival time after a period of treatment in descriptive statistics. The Multivariable Cox Proportional Hazards Model is a statistical method for comparing the

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proportional effect of several risk factors on survival. In the model, the measurement of effect is the hazard ratio (HR), which is the risk of failure, given that the participant has survived up to a specific time [66].

3.3 The Clinical Application of the NCSS in the Identification of Osteoporotic Fracture Patients

3.3.1 Study Participants

Using IMDB as our data source, we identified patients newly diagnosed with a hip or vertebral fracture between 2010 and 2014 as our study subjects, and defined them as "patients requiring treatment." The initial diagnosis date of a hip or vertebral fracture was defined as the index date of the study subject. Patients under 50 years in age, with a diagnosis of malignant neoplasm, osteoporotic fracture or Paget's disease or who had been prescribed with an anti-osteoporosis medications (AOMs) within one year prior to the index date, were excluded. The ICD-9-CM codes of identification for osteoporotic fracture patients are shown as Table 4.

Among them, we investigated the prescription pattern of the AOMs by distinguishing patients into those who began taking an AOM within one year after the index date, and those who did not. The AOMs is classified according to the hierarchical anatomical-therapeutic-chemical (ATC) code developed by the World Health Organization for drug utilization studies. The AOMs evaluated in this study included alendronate, denosumab, raloxifene teriparatide, and zoledronic acid. The system setting of the identification process used by the NCSS, the demographics of the study population, and the treatment pattern of the study population were presented quarterly. The ATC codes of anti-osteoporosis medications are shown as Table 5.

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Table 4. ICD-9-CM codes of identification for osteoporotic fracture patients

Diagnostic Category		ICD-9-CM Codes
Hip		820.x
Vertebral		805.x, 806.x
Paget's disease		731.0
Malignant neoplasm	Malignant neoplasm of lip, oral cavity, and pharynx	140.x–149.x
	Malignant neoplasm of digestive organs and peritoneum	150.x–159.x
	Malignant neoplasm of respiratory and intrathoracic organs	160.x–165.x
	Malignant neoplasm of bone, connective tissue, skin, and breast	170.x–175.x
	Kaposi's sarcoma	176.x–176.x
	Malignant neoplasm of genitourinary organs	179.x–189.x
	Malignant neoplasm of other and unspecified sites	190.x–199.x
	Malignant neoplasm of lymphatic and hematopoietic tissue	200.x–208.x

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Table 5. The ATC Code of Anti-Osteoporosis Medications

Drug Name	ATC Codes
Alendronate	M05BA04
Denosumab	M05BX04
Raloxifene	G03XC01
Teriparatide	H05AA02
Zoledronic acid	M05BA08

3.4 Investigating the Difference of Effectiveness and Safety between Non-vitamin K Antagonist Oral Anticoagulants and Warfarin in the Patients with Non-valvular Atrial Fibrillation

In this section, we use an example to demonstrate the clinical application of the NCSS, which is used to investigate the clinical effectiveness and safety between non-vitamin K antagonist oral anticoagulants (NOACs) and warfarin in patients with non-valvular atrial fibrillation (AF). According to clinical guidelines [67, 68], anticoagulant therapy is recommended for AF patients to prevent the risk of ischemic stroke, which is one of thromboembolism, one of the major complications of AF. Warfarin, a non-vitamin K antagonist, was the only option for oral anticoagulant treatment in AF patients for decades. Although warfarin is an effective treatment for ischemic stroke prevention, its therapeutic

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effect is complicated due to a narrow therapeutic range and multiple drug-food and drug-drug interactions [69-71]. These features lead to a requirement for monitoring to optimize the therapeutic dose to prevent the risk of adverse events, especially major bleeding [69, 70].

In recent years, the NOACs (i.e., dabigatran, rivaroxaban, and apixaban) have been launched and suggested as alternatives for warfarin. Compared to warfarin, the NOACs demonstrated similar or better stroke prevention effects and similar or lower risks of bleeding in clinical trials [72-74]. Moreover, the NOACs exhibit fewer drug-food or drug-drug interactions and do not require regular monitoring. Although the effectiveness and safety of NOACs have been proven in clinical trials, whether these effects observed in clinical trials translate well in "real-world" clinical practice have not been discussed. We aimed to investigate the clinical effectiveness and safety between NOACs and warfarin in patients with non-valvular AF within the NTUH clinical surveillance system.

3.4.1 Study Participants

We first identified patients who were at least 20 years old with AF but without a diagnosis of prosthetic heart valve or mitral valve disease between 2010 and 2015 as our study cohort of non-valvular AF patients. We further identified subjects who were newly prescribed anticoagulants, including warfarin, dabigatran, rivaroxaban and apixaban, in the study period. The ATC codes of NOACs and warfarin was present in Table 6. The first date of prescribing anticoagulants was defined as the index date of the study subject. Those subjects who had ever received any anticoagulants prescription or who were pregnant, diagnosed with cancer, or under chronic dialysis within one-year prior to the index date were excluded. We also exclude subjects prescribed NOACs along with warfarin on the index date.

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Table 6. ATC Codes of NOACs and Warfarin Medications

Drug Class	Drug Name	ATC Code
Warfarin	Warfarin	B01AA03
NOACs	Dabigatran	B01AE07
	Rivaroxaban	B01AF01
	Apixaban	B01AF02

The outcomes of interest, including transient ischemic attack (TIA), ischemic stroke, venous thromboembolism (VTE), and intracranial hemorrhage (ICH), are irreversible events. If subjects experienced these outcomes before the index date, the occurrence of these outcomes would not be related to the distinct effect between different treatments. To ensure that theses irreversible outcomes that occurred during the follow-up period were incident events, which refers to new occurred events, we identified four sub-cohorts for each irreversible outcomes and excluding those who had the irreversible outcomes within a one-year prior to the index date, and conducted statistical analysis separately. Finally, we stratified the subjects into two study groups, NOACs users and warfarin users in the original cohort and each sub-cohort.

3.4.2 Data Definition and Outcome Definition

The outcomes of interest in this study are clinical effectiveness and safety. Clinical effectiveness was defined as a transient ischemic attack (TIA), ischemic stroke and venous

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thromboembolism (VTE). Safety was defined as intracranial hemorrhage (ICH), gastrointestinal (GI) bleeding. All of these seven outcomes above were assessed separately in different cohort mentioned above during the follow-up period. Any diagnoses on the records of outpatients' visits, hospitalization and emergency room visits were applied for the assessment of the study outcomes. The outcome define of ICD-9-CM codes are shown as Table 7.

Table 7. Outcome Define of ICD-9-CM codes

Outcomes	**ICD-9-CM codes and diagnosis**
Ischemic stroke	433 Occlusion and stenosis of prevertebral arteries with cerebral infarction 434 Occlusion of cerebral arteries with cerebral infarction
Transient Ischemic Attack	435 Transient cerebral ischemia
Systemic Embolism	444 Arterial embolism and thrombosis
Venous Thromboembolism	451 Phlebitis and thrombophlebitis 453 Other venous embolism and thrombosis 415.1 Pulmonary embolism and infarction
Intracranial Hemorrhage	430 Subarachnoid hemorrhage 431 Intra-cerebral hemorrhage 432 Other and unspecified intracranial hemorrhage
Gastrointestinal Bleeding	531.0 Acute gastric ulcer with hemorrhage 531.2 Acute gastric ulcer with hemorrhage and perforation 531.4 Chronic or unspecified gastric ulcer with hemorrhage 531.6 Chronic or unspecified gastric ulcer with hemorrhage and perforation 532.0 Acute duodenal ulcer with hemorrhage 532.2 Acute duodenal ulcer with hemorrhage and perforation

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Outcomes	ICD-9-CM codes and diagnosis
	532.4 Chronic or unspecified duodenal ulcer with hemorrhage
	532.6 Chronic or unspecified duodenal ulcer with hemorrhage and perforation
	533.0 Acute peptic ulcer of unspecified site with hemorrhage
	533.2 Acute peptic ulcer of unspecified site with hemorrhage and perforation
	533.4 Chronic or unspecified peptic ulcer of unspecified site with hemorrhage
	533.6 Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and perforation
	534.0 Acute gastro-jejunal ulcer with hemorrhage
	534.2 Acute gastro-jejunal ulcer with hemorrhage and perforation
	534.4 Chronic or unspecified gastro-jejunal ulcer with hemorrhage
	534.6 Chronic or unspecified gastro-jejunal ulcer with hemorrhage and perforation
	562.02 Diverticulosis of small intestine with hemorrhage
	562.03 Diverticulitis of small intestine with hemorrhage
	562.12 Diverticulosis of colon with hemorrhage
	562.13 Diverticulitis of colon with hemorrhage
	569.3 Hemorrhage of rectum and anus
	569.85 Angiodyspasia of the intestine with hemorrhage
	578.1 Blood in stool
	578.9 Hemorrhage of GI tract, unspecified

In this practical example of the NCSS, we used both ITT and AT analyses. In ITT analysis, patients were followed from the index date to the following events: 1) occurrence of the outcome of interest, or 2) the end of two-year follow-up since the index date, whichever came first. In the AT analysis, patients were followed from the index date to the following events: 1)

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occurrence of the outcome of interest, 2) discontinuation of the index anticoagulant, or 3) the end of two-year follow-up since the index date, whichever came first. Medication discontinuation was defined as either discontinuing oral anticoagulation therapy or having a greater than 30-day gap between the end of an oral anticoagulant prescription and the next prescription.

3.4.3 Baseline Characteristics and Covariates

The covariates adjusted were those factors known to affect anticoagulant treatment and study outcomes, including age, gender, annual stroke risk, specific comorbidities, and concomitant medications. Comorbidities were identified by diagnoses made within 12 months before the index date, and the comorbidities define of ICD-9-CM codes are shown as Table 8. Concomitant medications were identified by at least one prescription within 12 months preceding the index date, and the concomitant medications definition of ATC codes are shown as Table 9.

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Table 8. Comorbidities define of ICD-9-CM codes

Diagnosis	ICD-9-CM codes and diagnosis
Prosthetic heart valve	V42.2 heart valve replaced by transplant V43.3 heart valve replaced by a mechanical device 353.0 closed heart valvotomy 35.2 open and other replacement of heart valve
Heart valve related disorder	394 disease of mitral valve 396 disease of mitral and aortic valves 424.0 mitral valve disorder
Pregnancy	V22 Normal pregnancy
Chronic dialysis	V45.1 postsurgical renal dialysis status V56 encounter for dialysis and dialysis catheter care 39.95 hemodialysis 54.98 peritoneal dialysis
Cancer	140–149 Malignant neoplasm of lip, oral cavity, and pharynx 150–159 Malignant neoplasm of digestive organs and peritoneum 160–165 Malignant neoplasm of respiratory and intrathoracic organs 170–175 Malignant neoplasm of bone, connective tissue, skin, and breast 176–176 Kaposi's sarcoma 179–189 Malignant neoplasm of genitourinary organs 190–199 Malignant neoplasm of other and unspecified sites 200–208 Malignant neoplasm of lymphatic and hematopoietic tissue

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Table 9. Concomitant medications define of ATC codes

Medications	ATC code
Antiplatelet drugs	B01AC
Proton-pump inhibitor	A02BC
H2 receptor antagonist	A02BA
Other antacids	A02A
NSAIDs	M01A
Antiarrhythmic drugs	C01B
Digoxin	C01AA05
Beta-blockering agents	C07A
Dihydropyridine calcium channel blockers	C08C
Non-dihydropyridine calcium channel	C08D
Statins	C10AA
Anti-diabetes drugs	A10
ARBs/ACEIs	C09

3.4.4 Statistical Analysis Method

One-to-one propensity score matching using a nearest-neighbor matching algorithm with a maximum matching caliper of 0.2 was applied to balance the covariates of baseline

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characteristics between the NOACs and warfarin groups. Absolute standardized mean differences were applied to compare the between-group balance of the baseline characteristics. An absolute standardized difference of less than 0.1 was recognized as indicating no significant difference. Two kinds of survival analysis, Kaplan-Meier Curve and Cox-proportional hazard models, were applied to determine the relationship between anticoagulant treatment and study outcomes. Two-sided tests with an $\alpha < 0.05$ were defined as statistically significant. All statistical procedures were performed by NCSS.

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Chapter 4. Results

4.1 The Clinical Application of the NCSS in the Identification of Osteoporotic Fracture Patients

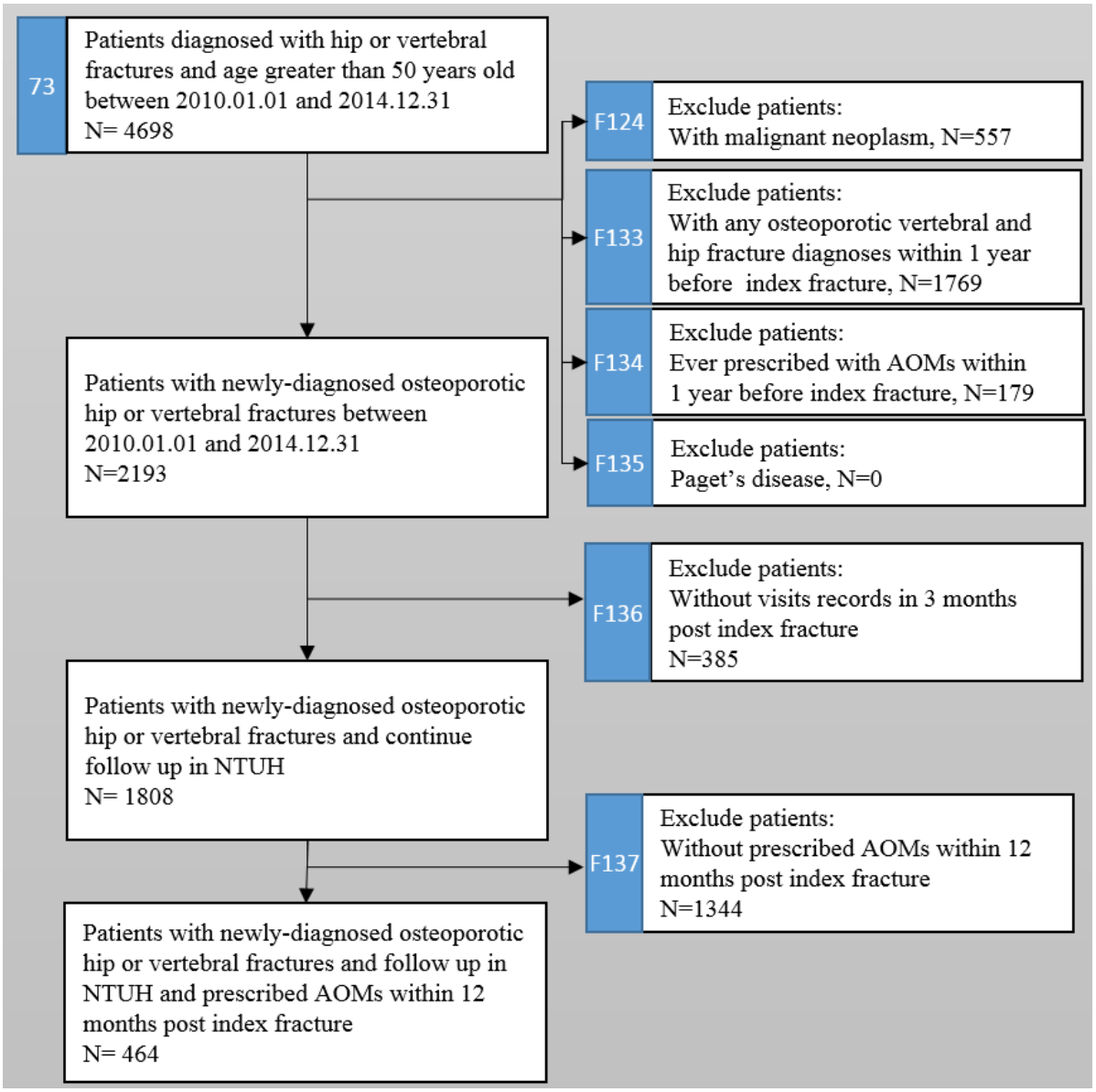

Figure 5. Study flow chart implemented by NCSS.

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The NCSS design uses a protocol-based standardized process of incremental development, testing, and deployment to meet specific clinical needs. We demonstrated a practical example of identifying the unmet treatment needs for patients encountering major osteoporotic fractures, and implemented the hierarchical study population using the NCSS, as depicted in Figure 5.

This study flow contains seven Identification processes. Each identification process had been assigned a universally unique identifier with a case number (marked by the blue background, such as 73, F124, F133, F134, F135, F136, and F137). The case number with an *F* as a prefix stands for its own hierarchical structure. A hierarchical structure means that the researcher reused the patient list for an Identification process. For example, the case F124 selected case 73 as its patient data source for the Identification process.

We initially selected older patients diagnosed with a hip or vertebral fracture between 2010 and 2014. By adopting the identification and filter function of the NCSS, patients with a history of malignant neoplasm (N = 557), or osteoporotic vertebral and hip fracture (N = 1,769) within 1 year prior to the index date, were excluded. In addition, to identify a new AOM user, we excluded 179 patients with an AOM prescription before the index date. We identified 2,193 incidence cases for hip or vertebral fractures within the period of 2010–2014. These patients were defined as “patients requiring treatment” according to the current treatment guidelines. In addition, each patient list can be viewed visualized summary statistics in Report Service, as depicted in Figure 6.

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Characteristics | Longitudinal Incidence Trend | Source Record

Sync Record	ID	Patient List	Label	Number Of Included Patients	Number of Excluded Patients
View	73		[Osteoporotic Fracture] Incident Case	4,698	0
View	F124	73	[Osteoporotic Fracture] exclude malignant neoplasm	4,141	557
View	F133	F124	[Osteoporotic Fracture] exclude osteoporotic fracture within 1 year prior to index	2,372	1,769
View	F134	F133	[Osteoporotic Fracture] exclude AOMs	2,193	179
View	F135	F134	[[Osteoporotic Fracture] exclude Paget's Disease	2,193	0
View	F136	F135	[Osteoporotic Fracture] visit within 3 month post index	1,808	385
View	F137	F136	[Osteoporotic Fracture] initiated AOMs within 1 year post index	464	1,344

Figure 6. Snapshot of a Source Record in NCSS.

Through the Source Record we can get the Number of Included (and Excluded) Patients and the data source (Patient List). For example, case number F137's identification result of the Number of included patients is 464 and the Number of excluded patients is 1344. Because of the Hierarchical structure, we can follow the F137 patient list to find its data source F136. This process will keep running and finally find the root 73. Finally, we can get a source record report.

To ensure those participants having a continuous follow-up, we excluded 385 patients who had not visited the hospital within 3 months after the index date. We enrolled in the study 1,808 patients who had continued to follow-up at NTUH within 3 months' post index date of their fracture. To investigate the prescription pattern of the AOMs, we established two groups that were classified based on their AOM prescription date, and by adopting a filter function, we identified 1,808 (82.4%) patients who continued to follow-up at NTUH, and 464 (21.2%)

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patients prescribed with an AOM, within 3 and 12 months post index date of their fracture, respectively.

The NCSS provided a summary of the baseline characteristics of the study population including gender, age, BMI, socioeconomic status, occupation types, and marital status, as shown in Figure 7. For example, among the patients who began taking an AOM within 1 year after the index date, their mean age was 76.47 ± 10.10 and their mean BMI was 22.95 ± 3.86 kg/m^2; in addition, the proportion of females was 82.76% (n = 384). This population showed a high proportion of married patients (74.22%) with a normal income level (99.78%). NCSS provided information regarding the drug utilization of AOMs for the study population.

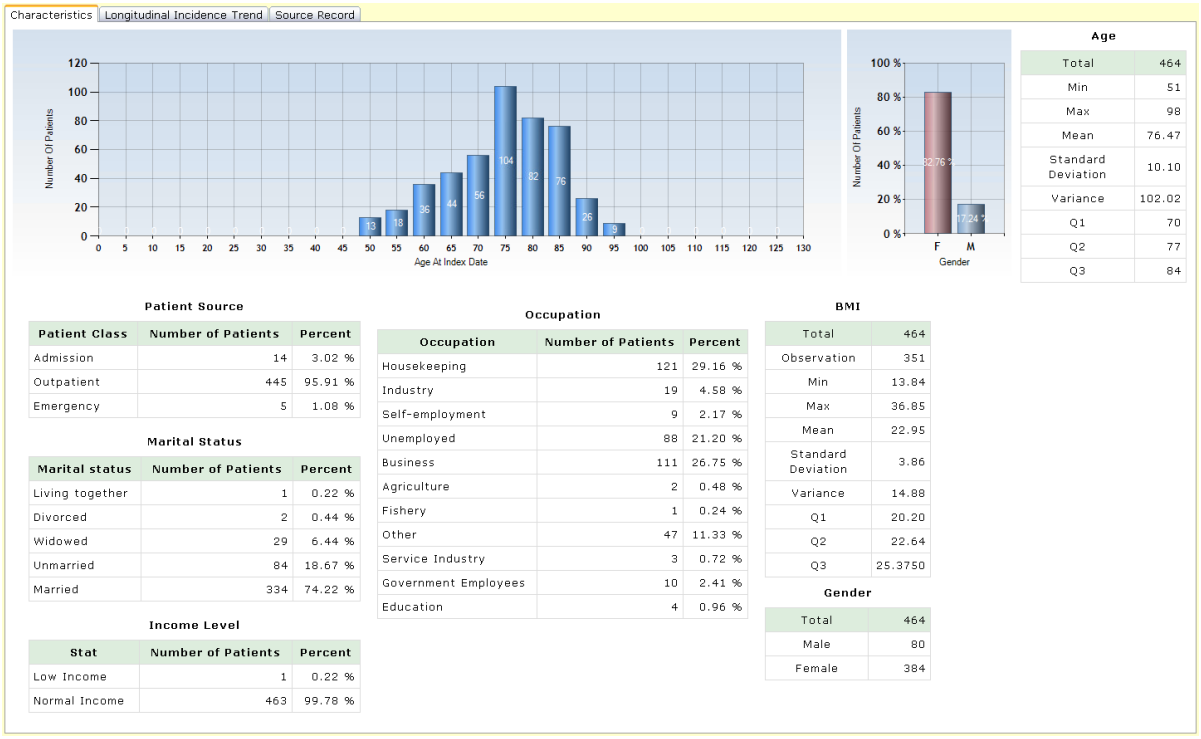

Figure 7. Snapshot of Report of characteristics in NCSS.

The longitudinal trends of patients newly diagnosed with an osteoporotic fracture and those who began taking an AOM within 1-year post index date of their fracture are illustrated in Figure 8. For example, taking the information from Figure 8(a), we found that there were

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approximately 130 newly diagnosed osteoporotic fracture patients continuing their follow-up at NTUH in 2014Q4, and among them, 42 (32.3%) began taking an AOM within 1-year post index date of their fracture.

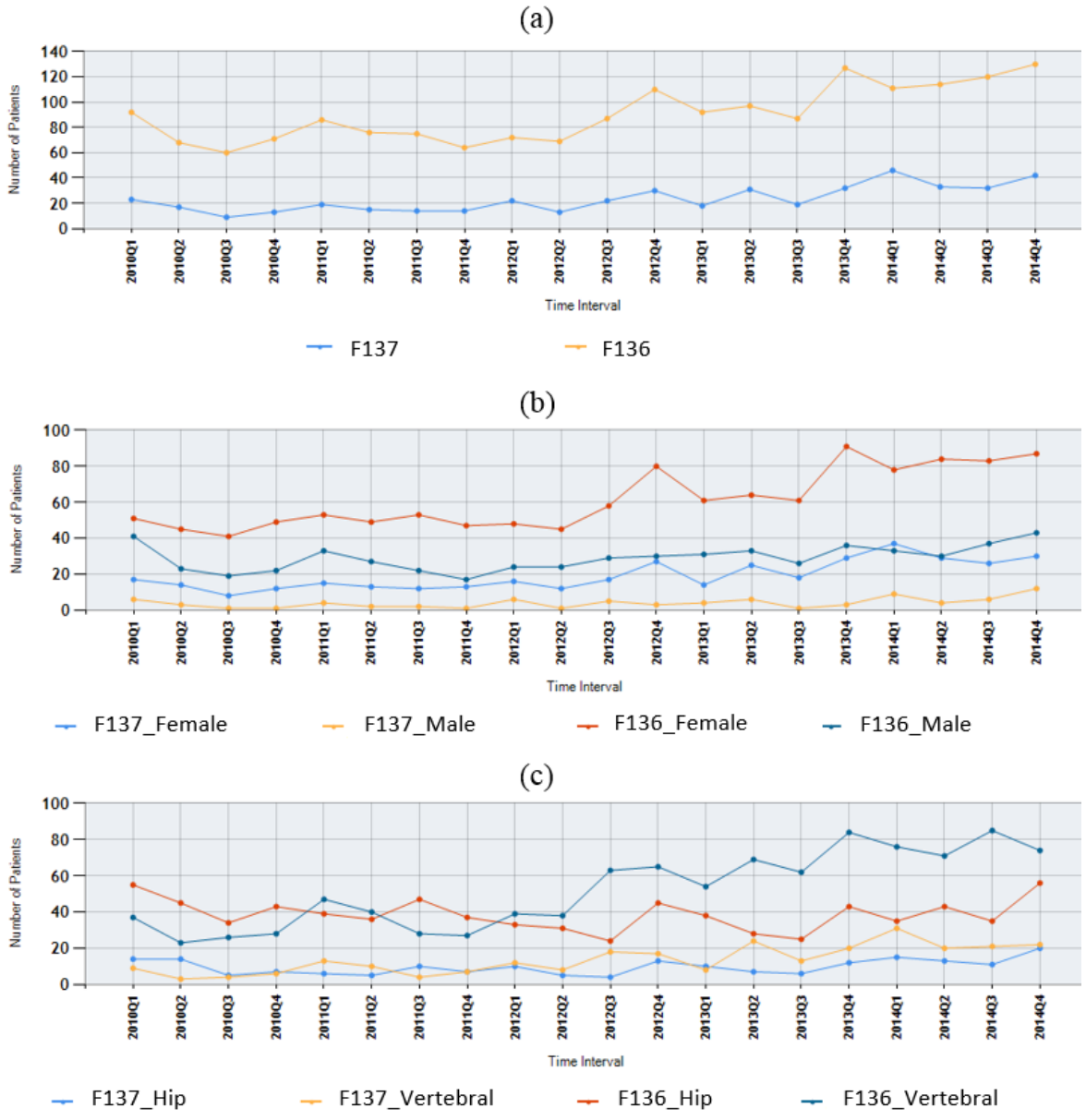

Figure 8. Snapshot of quarterly report for incidence trend of study cohorts.

Furthermore, the NCSS provides the choice of information stratification based on gender, index date, fracture type, and other types of information, which can provide monthly, quarterly, and yearly, thereby increasing the flexibility of the clinical interpretation. For example, as

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shown in Figure 8(b), there were 87 female and 43 male fracture patients in 2014Q4, and among them, 30 (35%) females and 12 (28%) males began taking an AOM within 1-year post index date of their fracture. Information on patients with different fracture types can be seen in Figure 8(c).

4.2 Investigating the Clinical Effectiveness and Safety between Non-vitamin K Antagonist Oral Anticoagulants and Warfarin in Patients with Non-valvular Atrial Fibrillation

We demonstrated a practical example of investigating the difference of effectiveness and safety between NOACs and warfarin in the patients with non-valvular AF, and implemented the hierarchical study population using the NCSS, as depicted in Figure 1. We initially identified 9,207 AF patients who were 20 years old or older between 2010 and 2015. Approximately 90 % (N = 8,263) of these patients were Non-valvular AF patients. By adopting the identification and filter function of the NCSS, patients without an oral anticoagulant prescription during the study period (N = 4,767), or with cancer (N = 234), pregnancy (N = 0) and chronic dialysis (N = 1) within 1-year prior to index date were excluded. In addition, to identify new oral anticoagulants user, we excluded 907 patients with an oral anticoagulants prescription before the index date. Overall, we included 2,357 AF patients with newly prescribed oral anticoagulant between 2010 and 2015. The study flow chart of the NCSS is depicted in Figure 9.

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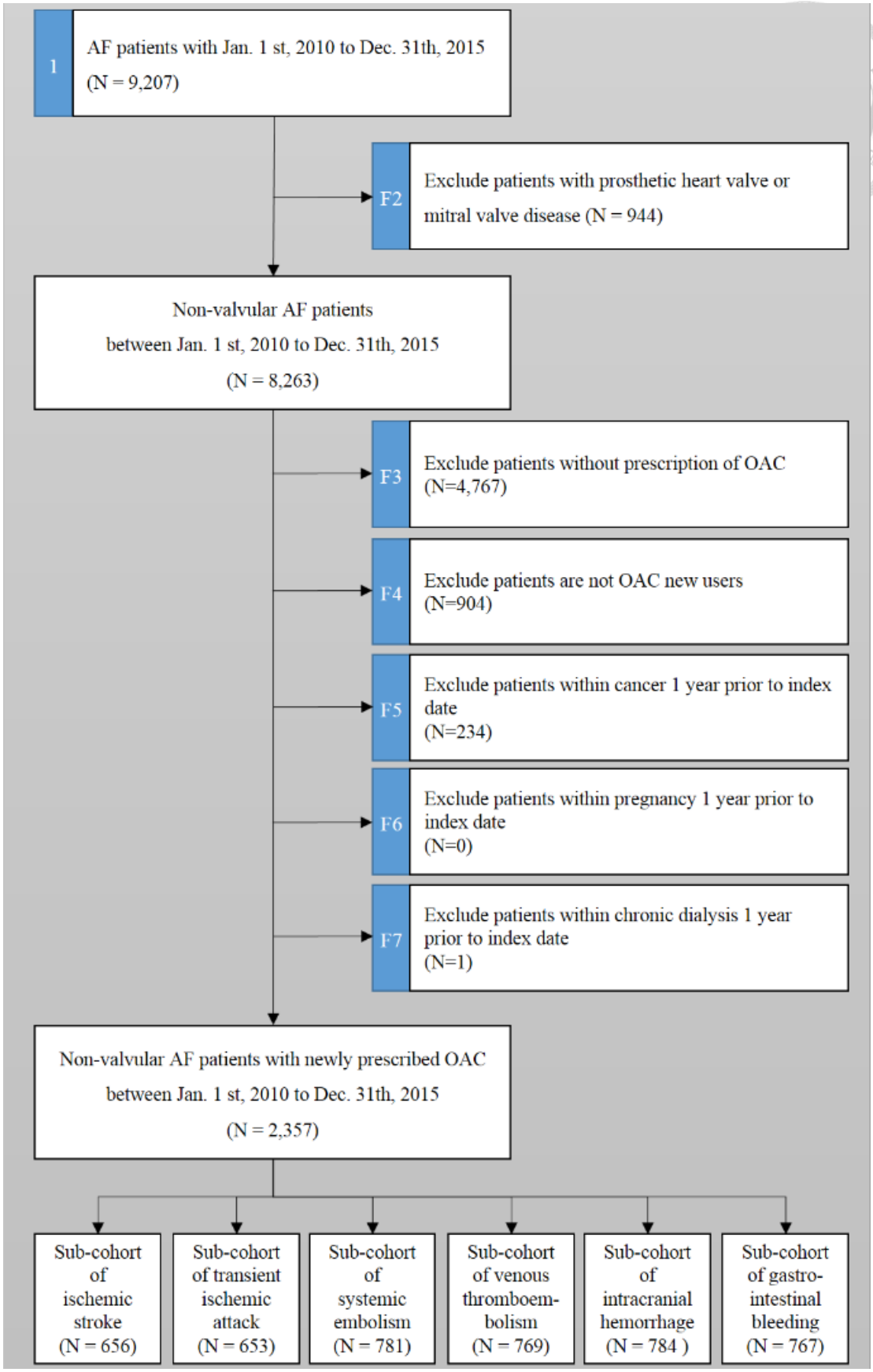

Figure 9. Study flow chart of AF patients with newly prescribed oral anticoagulant.

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This study flow contains seven identification processes. Each identification process had been assigned a universally unique identifier with a case number (marked by the blue background, such as 1, F2, F3, F4, F5, F6, and F7). The outcomes of interest in this study are clinical effectiveness and safety. Clinical effectiveness was defined as TIA, ischemic stroke, systemic embolism and VTE. Safety was defined as in ICH, GI bleeding. All of these six outcomes above were assessed separately in different cohort mentioned above during the follow-up period. Any diagnoses on the records of outpatients' visits, hospitalization and emergency room visits were applied for the assessment of the study outcomes.

Since most of the sub-cohort are similar, we only show the sub-cohort of ischemic stroke in this study. The sub-cohort of ischemic stroke contains two identification process (F8, and F9), one Mapping Data Model process (G1), one Propensity Score Matching process (B1) and one Survival Analysis process (O1). In the sub-cohort of ischemic stroke, we further excluded subjects (F8) who experienced ischemic stroke or TIA within 1-year prior to the index date (N = 359) from original cohort and categorized (G1) them into NOACs group (N = 1,023) and warfarin group (N = 975) according to their first oral anticoagulants at index date. After propensity score matching (B1), the final sample contained 656 NOACs-warfarin matched pairs. The study flow of sub-cohort of ischemic stroke is depicted in Figure 10.

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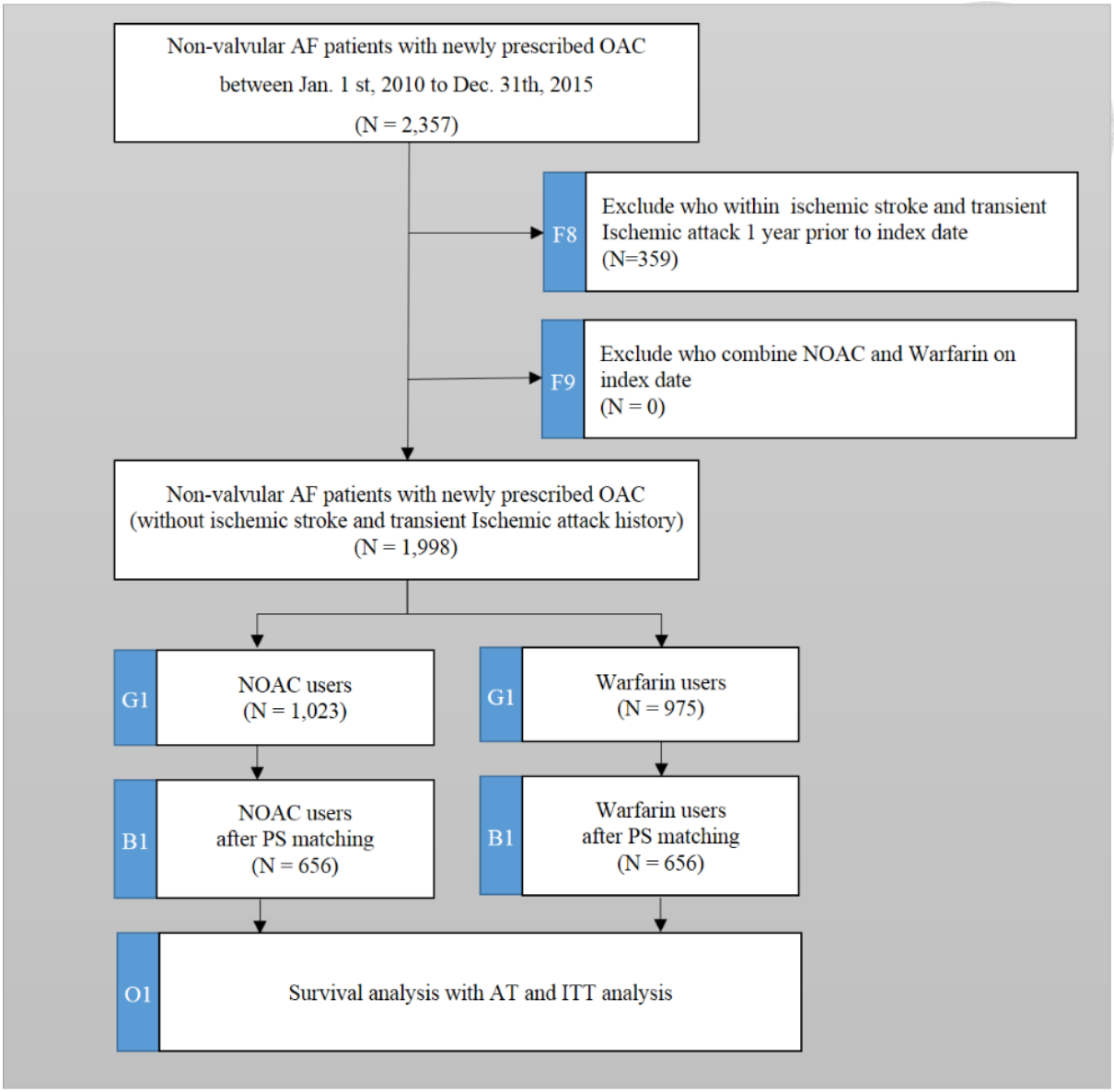

Figure 10. The study flow of sub-cohort of ischemic stroke.

The detail of baseline characteristics before and after matching for sub-cohort of ischemic stroke were presented in Figure 11 and Figure 12. The red word is shown as the standardized mean differences (SMD) greater than 0.2 in Figure 11, including age between 70 and 74 years old (19.3% vs. 11.5%), (31.2% vs. 18.9%), antiplatelet drug (51.2% vs. 38.4%), and renal disease (2.4% vs. 7.1%). After propensity score matching (B1), the SMD in each variable were

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less than 0.1, which showed a good between-group balance of baseline characteristics, were presented in Figure 12.

Before Propensity Score Matching

	NOAC	Warfarin	SMD
n	1023	975	
ARBs/ACEIs = 1 (%)	481 (47.0)	378 (38.8)	0.167
Acute myocardial infarction = 1 (%)	24 (2.3)	12 (1.2)	0.084
Age 65-69 = 1 (%)	166 (16.2)	138 (14.2)	0.058
Age 70-74 = 1 (%)	197 (19.3)	112 (11.5)	0.217
Age 75-79 = 1 (%)	208 (20.3)	123 (12.6)	0.209
Age <65 = 1 (%)	133 (13.0)	418 (42.9)	0.706
Age >=80 = 1 (%)	319 (31.2)	184 (18.9)	0.287
Antiplatelet drugs = 1 (%)	524 (51.2)	374 (38.4)	0.261
Coagulation deficiency = 1 (%)	1 (0.1)	2 (0.2)	0.028
Diabetes = 1 (%)	236 (23.1)	168 (17.2)	0.146
Digoxin = 1 (%)	124 (12.1)	131 (13.4)	0.039
Dihydropyridine calcium channel blockers = 1 (%)	356 (34.8)	257 (26.4)	0.184
GI bleeding = 1 (%)	25 (2.4)	23 (2.4)	0.006
Gender = 1 (%)	427 (41.7)	378 (38.8)	0.061
H2 receptor antagonist = 1 (%)	105 (10.3)	87 (8.9)	0.046
Heart failure = 1 (%)	176 (17.2)	162 (16.6)	0.016
Hypertension = 1 (%)	514 (50.2)	406 (41.6)	0.173
Intracranial hemorrhage = 1 (%)	7 (0.7)	4 (0.4)	0.037
Liver disease = 1 (%)	34 (3.3)	45 (4.6)	0.066
NSAIDs = 1 (%)	150 (14.7)	136 (13.9)	0.020
Non-dihydropyridine calcium channel blockers = 1 (%)	147 (14.4)	133 (13.6)	0.021
Other antacids = 1 (%)	275 (26.9)	273 (28.0)	0.025
Peptic ulcer disease = 1 (%)	54 (5.3)	43 (4.4)	0.040
Peripheral vascular disease = 1 (%)	16 (1.6)	17 (1.7)	0.014
Proton-pump inhibitor = 1 (%)	98 (9.6)	120 (12.3)	0.087
Renal disease = 1 (%)	25 (2.4)	69 (7.1)	0.219
Statins = 1 (%)	240 (23.5)	160 (16.4)	0.177
Venous Thromboembolism = 1 (%)	9 (0.9)	12 (1.2)	0.034
anti-diabetes drugs = 1 (%)	191 (18.7)	155 (15.9)	0.073
antiarrhythmic drugs = 1 (%)	388 (37.9)	393 (40.3)	0.049
beta-blockering agents = 1 (%)	449 (43.9)	431 (44.2)	0.006

Figure 11. Basic characteristics of the sub-cohort of ischemic stroke before Propensity Score Matching.

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After Propensity Score Matching

	NOAC	Warfarin	SMD
n	656	656	
ARBs/ACEIs = 1 (%)	266 (40.5)	265 (40.4)	0.003
Acute myocardial infarction = 1 (%)	10 (1.5)	10 (1.5)	<0.001
Age 65-69 = 1 (%)	122 (18.6)	126 (19.2)	0.016
Age 70-74 = 1 (%)	113 (17.2)	106 (16.2)	0.029
Age 75-79 = 1 (%)	118 (18.0)	114 (17.4)	0.016
Age <65 = 1 (%)	132 (20.1)	139 (21.2)	0.026
Age >=80 = 1 (%)	171 (26.1)	171 (26.1)	<0.001
Antiplatelet drugs = 1 (%)	256 (39.0)	267 (40.7)	0.034
Coagulation deficiency = 1 (%)	1 (0.2)	2 (0.3)	0.032
Diabetes = 1 (%)	131 (20.0)	127 (19.4)	0.015
Digoxin = 1 (%)	84 (12.8)	95 (14.5)	0.049
Dihydropyridine calcium channel blockers = 1 (%)	191 (29.1)	192 (29.3)	0.003
GI bleeding = 1 (%)	19 (2.9)	14 (2.1)	0.049
Gender = 1 (%)	274 (41.8)	266 (40.5)	0.025
H2 receptor antagonist = 1 (%)	60 (9.1)	62 (9.5)	0.010
Heart failure = 1 (%)	104 (15.9)	117 (17.8)	0.053
Hypertension = 1 (%)	295 (45.0)	298 (45.4)	0.009
Intracranial hemorrhage = 1 (%)	5 (0.8)	4 (0.6)	0.018
Liver disease = 1 (%)	26 (4.0)	22 (3.4)	0.032
NSAIDs = 1 (%)	100 (15.2)	102 (15.5)	0.008
Non-dihydropyridine calcium channel blockers = 1 (%)	85 (13.0)	89 (13.6)	0.018
Other antacids = 1 (%)	202 (30.8)	194 (29.6)	0.027
Peptic ulcer disease = 1 (%)	34 (5.2)	35 (5.3)	0.007
Peripheral vascular disease = 1 (%)	11 (1.7)	15 (2.3)	0.044
Proton-pump inhibitor = 1 (%)	81 (12.3)	80 (12.2)	0.005
Renal disease = 1 (%)	24 (3.7)	23 (3.5)	0.008
Statins = 1 (%)	106 (16.2)	121 (18.4)	0.060
Venous Thromboembolism = 1 (%)	6 (0.9)	8 (1.2)	0.030
anti-diabetes drugs = 1 (%)	112 (17.1)	104 (15.9)	0.033
antiarrhythmic drugs = 1 (%)	245 (37.3)	246 (37.5)	0.003
beta-blockering agents = 1 (%)	276 (42.1)	279 (42.5)	0.009

Figure 12. Basic characteristics of the sub-cohort of intracranial hemorrhage after Propensity Score Matching.

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Kaplan–Meier survival plots of ischemic stroke with AT and ITT analysis are in Figure 16 and Figure 17 that involve computing of survival probability of two year follow up time. The warfarin users were lower survival probability than NOACs users.

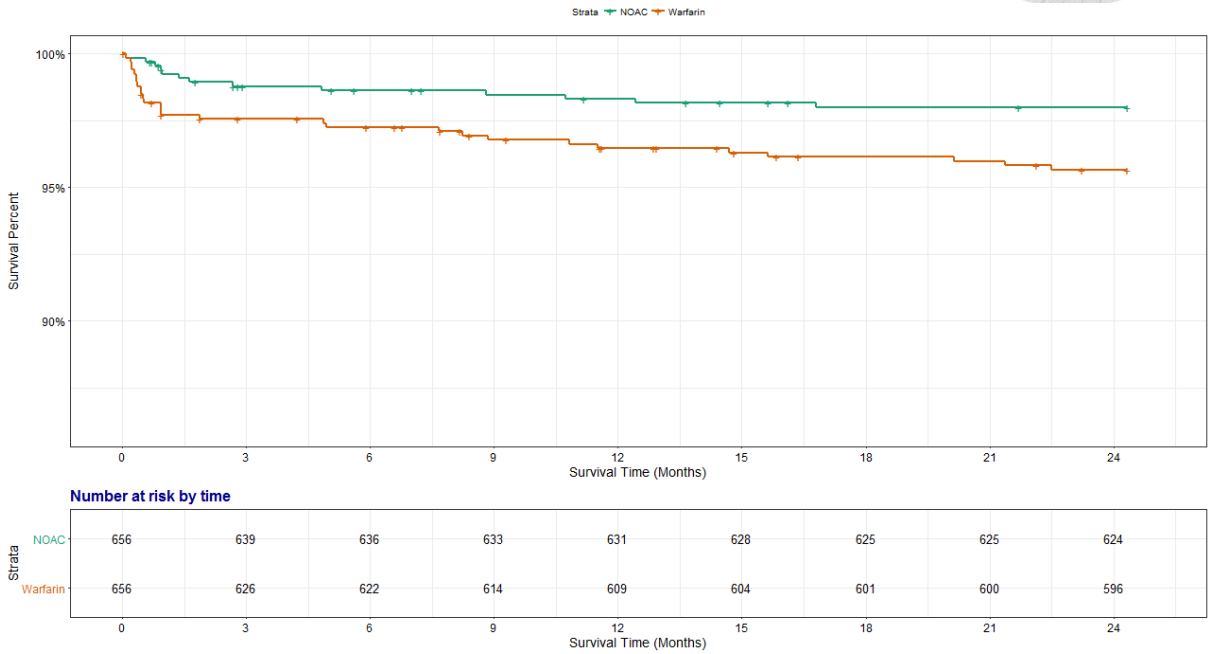

Figure 13. Kaplan–Meier Survival Plots of ischemic stroke with ITT analysis.

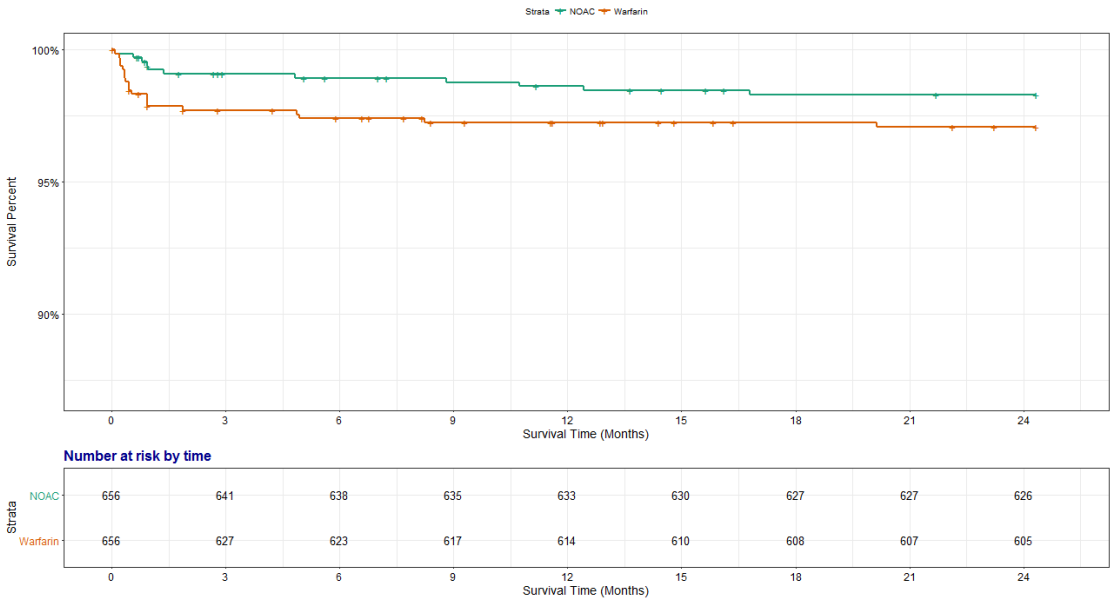

Figure 14. Kaplan–Meier Survival Plots of ischemic stroke with AT analysis.

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Table 10 and Table 11 show six outcomes of descriptive analytics that incidence of outcomes after two years of follow-up with ITT analysis and AT analysis, including ischemic stroke, TIA, systemic embolism, VTE, ICH and GI bleeding.

Table 10. The incidence of outcomes with ITT analysis

Group	Outcome	N	Events	Follow up Duration (Patient - Days)	Incidence Density	Cumulative Incidence
Warfarin	Ischemic stroke	656	28	446,943	6.26	4.27%
NOACs	Ischemic stroke	656	13	461,354	2.82	1.98%
Warfarin	TIA	653	11	453,341	2.43	1.68%
NOACs	TIA	653	10	461,323	2.17	1.53%
Warfarin	Systemic embolism	781	14	547,398	2.56	1.79%
NOACs	Systemic embolism	781	7	553,087	1.27	0.90%
Warfarin	VTE	769	8	541,968	1.48	1.04%
NOACs	VTE	769	4	547,292	0.73	0.52%
Warfarin	ICH	784	3	550,999	0.54	0.38%
NOACs	ICH	784	4	556,467	0.72	0.51%
Warfarin	GI bleeding	767	33	525,090	6.28	4.30%
NOACs	GI bleeding	767	30	533,344	5.62	3.91%

Table 10 shows ITT analysis that warfarin users exhibited the higher crude incidence density (per 100,000 patient-years) than NOACs users, including ischemic stroke (warfarin: 6.26 events; NOACs: 2.82 events), TIA (warfarin: 2.43 events; NOACs: 2.17 events), Systemic embolism (warfarin: 2.56 events; NOACs: 1.27 events) and VTE (warfarin: 1.48 events;

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NOACs: 0.73 events). However, warfarin users had the lower crude incidence rates than NOACs users, including ICH (warfarin: 0.54 events; NOACs: 0.72 events) and GI bleeding (warfarin: 6.28 events; NOACs: 5.62 events).

Table 11. The incidence of outcomes with AT analysis

Group	Outcome	N	Events	Follow-up Duration (Patient - Days)	Incidence Density	Cumulative Incidence
Warfarin	Ischemic stroke	656	19	177,980	10.68	2.90%
NOACs	Ischemic stroke	656	11	167,508	6.57	1.68%
Warfarin	TIA	653	5	176,647	2.83	0.77%
NOACs	TIA	653	10	169,809	5.89	1.53%
Warfarin	Systemic embolism	781	5	231,202	2.16	0.64%
NOACs	Systemic embolism	781	6	204,214	2.94	0.77%
Warfarin	VTE	769	6	226,646	2.65	0.78%
NOACs	VTE	769	3	206,133	1.46	0.39%
Warfarin	ICH	784	1	230,972	0.43	0.13%
NOACs	ICH	784	4	208,929	1.91	0.51%
Warfarin	GI bleeding	767	18	218,166	8.25	2.35%
NOACs	GI bleeding	767	20	204,138	9.8	2.61%

Table 11 shows AT analysis that warfarin users had the higher crude incidence density than NOACs users, including ischemic stroke (warfarin: 10.68 events; NOACs: 6.57 events), VTE (warfarin: 2.65 events; NOACs: 1.46 events). However, warfarin users had the lower crude incidence rates than NOACs users, including TIA (warfarin: 2.83 events; NOACs: 5.89

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events), systemic embolism (warfarin: 2.16 events; NOACs: 2.94 events), ICH (warfarin: 0.43 events; NOACs: 1.91 events) and GI bleeding (warfarin: 8.25 events; NOACs: 9.8 events).

The results of adjusted Cox proportional hazards models are summarized in Table 12 and Table 13. After the 2-year follow-up, compared to warfarin users, NOACs users have a significantly lower risk of ischemic stroke after adjusting for age, sex, comorbidity and co-medication in ITT analysis (adjusted HR=0.41, P = 0.01) but have a comparable risk in AT analysis (adjusted HR = 0.54, P = 0.12).

Table 12. The hazard ratio of outcomes with ITT analysis

Group	Outcome	N	Events	Hazard ratio	P value	Confidence interval
Warfarin	Ischemic stroke	656	28	1		
NOACs	Ischemic stroke	656	13	0.41	0.01	0.21 - 0.82
Warfarin	TIA	653	11	1		
NOACs	TIA	653	10	0.99	0.99	0.41 - 2.41
Warfarin	Systemic embolism	781	14	1		
NOACs	Systemic embolism	781	7	0.44	0.09	0.17 - 1.15
Warfarin	VTE	751	8	1		
NOACs	VTE	751	4	0.49	0.25	0.14 - 1.68
Warfarin	ICH	784	3	1		
NOACs	ICH	784	4	1.42	0.68	0.26 - 7.82
Warfarin	GI bleeding	767	33	1		
NOACs	GI bleeding	767	30	1.01	0.98	0.61 - 1.67

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Table 13. The hazard ratio of outcomes with AT analysis

Group	Outcome	N	Events	Hazard ratio	P value	Confidence interval
Warfarin	Ischemic stroke	656	19	1		
NOACs	Ischemic stroke	656	11	0.54	0.12	0.25 - 1.16
Warfarin	TIA	653	5	1		
NOACs	TIA	653	10	1.95	0.24	0.65 - 5.87
Warfarin	Systemic embolism	781	5	1		
NOACs	Systemic embolism	781	6	1.34	0.65	0.371 - 4.86
Warfarin	VTE	751	6	1		
NOACs	VTE	751	3	0.53	0.37	0.13 - 2.21
Warfarin	ICH	784	1	1		
NOACs	ICH	784	4	254.16	0.15	0.16 - 478097.30
Warfarin	GI bleeding	767	18	1		
NOACs	GI bleeding	767	20	1.23	0.53	0.64 - 2.38

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Chapter 5. Discussion

5.1 Preliminary Findings

To the best of our knowledge, NCSS is a pioneering electronic clinical surveillance system in its attempt to organize decision-making activities and facilitate the standards-based process for clinical needs in Taiwan. In this study, we have successfully demonstrated two practical examples of two NCSS applications. The results of this study confirm that the NCSS is a feasible and useful approach to enable systematic analysis of evaluating the safety and effectiveness of drugs for clinical needs.

We can efficiently and correctly gather information on those patients requiring disease treatment and understand their treatment patterns, as well as identify any unmet treatment requirements in the hospital. Through this practical example of identification of osteoporotic fracture patients, we found that the pharmacological treatment rate of patients with an osteoporotic fracture is suboptimal at NTUH. On average, only 35% of female and 28% of male osteoporotic fracture patients initiated AOM therapy to prevent a subsequent fracture. More effort is warranted to improve the quality of care with these patients.

In practical example of investigating difference of effectiveness and safety between NOACs and warfarin in the patients with AF, we found that the NOACs users have a significantly lower risk of ischemic stroke compared with warfarin users but had a comparable risk of ICH in ITT analysis. This result regarding clinical effectiveness was very similar to the pivotal clinical trials of NOACs and some of the observational study with ITT design for outcome approach [72, 73]. Regarding AT analysis, we found that both the risk of ischemic

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stroke and ICH are similar between NOACs and warfarin users. Because the AT analysis states that the treatment assignment is based on the actual treatment the patients receive, patients who discontinued their index anticoagulant were stopped follow-up and become censor data [60-63]. The definition of treatment exposure is more closed to the real world situation, in which patients may discontinue or change their treatment. However, the total following time and frequency of the events in the AT analysis are less than ITT analysis. The AT analysis may not have enough statistical power to test the hypothesis, especially when the outcome is rare event. In our practical example, there is only one ICH event in warfarin group, so the HR is extremely large (adjusted HR=254.15, P = 0.15) but not have any statistical significance with insufficient statistical power.

5.2 Comparison with Prior Work

Clinical surveillance systems have been widely implemented [10, 32, 41, 42, 47, 48, 75], and studies have demonstrated the use of various algorithms to identify potential research patient cohorts. There are several important core concepts include cohort identification, clinical orders query, data visualization, data mart, hierarchical filter, statistical adjustment and signal detection. We discuss their definitions or functions as the following:

(i) Cohort identification: It has the ability to screen or identify potential study participants for study planning and retrospective review.

(ii) Clinical orders query: User can search the detailed information about such as the diagnosis (ICD-9 or ICD-10), medication (ATC code) in the integrated interface.

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(iii) Data visualization: It has the ability to access the clinical data for research purposes and clarifying the characteristics of study population by visualization.

(iv) Data mart: It has the ability to provide the specific dataset that allows users to have access to the structured data and reduce the computation overhead.

(v) Hierarchical filter: It has the ability to screen and generate a new study population that can adopt a patient list from data mart as their patient data source to query the next identification process continuously.

(vi) Statistical adjustment: It has the ability to reduce or eliminate selection bias in observational studies by balancing covariates (the characteristics of participants) between treated and control groups.

(vii) Signal detection: It has the ability to identify unexpected potential associations between medical product exposures and health outcomes of interest in a real-world population.

In Table 14, we list these features and compare several internationally renowned clinical surveillance systems that were designed to monitor the safety profile of products in the postmarketing environment, including Sentinel [47] mandated by FDA in the US, AsPEN [41] collaborated among the Asian countries, and EU-ADR [42] funded by the European Commission.

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Table 14. Proposed features to include in a definition of surveillance of a health-care product for comparison

	Our study	**Sentinel [47]**	**AsPEN [41]**	**EU-ADR [42]**
Cohort identification	Y	Y	Y	Y
Clinical orders query	Y			Y
Data visualization	Y		Y	Y
Data mart	Y			
Hierarchical filter	Y			
Statistical adjustment	Y	Y	Y	
Signal detection	Y	Y	Y	Y

The Sentinel and AsPEN is based on offline operations using SAS software that have developed a series of macro for a distributed database, and the EU-ADR have developed a desktop software to aggregate data to a central repository. Our proposed system is online and interoperable platform to query a central database.

The above four systems can perform the key functions of cohort identification, however, only our system and the EU-ADR can query a series of clinical orders further. The medical coding systems play a significant role in clinical research, and they are advancing with time. However, the Sentinel and AsPEN systems based on SAS file that are lack of interactivity,

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which means that the algorithm of cohort identification need to be imported from outside. Considering the cohesion of the system, we think that integrated coding systems to interoperable platform can bring more advantages, for example, reduce input error, improve search efficiency, and advance user experience. The NCSS integrates the workflow of cohort identification to accelerate the survey process based on certain guidelines. In particular, for quality assurance, clinical researchers or medical policymakers need to monitor specific quality indicators to ensure the quality of patient care. However, the others systems have not proposed how to integrate a protocol-based process in the building of a cohort discovery. The clinical surveillance systems should also have the capability to bring guidelines to clinical practitioners. The clinical practitioners can focus on clinical needs to achieve a continuous process integration using standardized NCSS templates.

The different clinical contexts can be refined using a new scaffold to meet clinical needs based on the original standardized templates. In fact, different methodologies of capturing cases of patients would result in disparate estimates of incidence or mortality. For example, how to identify patients with severe sepsis. There are four ways available [76-79] including Angus et al., Martin et al., Dombrovskiy et al., and Wang et al. We believe this clinical knowledge should be preserved and converted into a shareable template for a collaborative research network. These templates can be quickly searched and reused for inclusion/exclusion criteria of patient identification in the Template Library. Therefore, the researchers can embrace change courageously because they only need to focus on any existing differences. More importantly, these processes should be conceptualized as continuous organizational efforts to lead to self-organizing innovation of the NCSS.

Another strength of our NCSS system is that the hierarchical structure of the system design has not been implemented in the other systems. We designed a mechanism to enhance the

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scalability and reusability for reusing the tree-based patient list in Data Mart. We think other researchers can reuse identified list of patients. Especially, for the design of a subgroup study or have a similar context of research. In order to better interpret the process of identification of each patient list, we designed a hierarchical structure where each patient list could be traced back to its patient data source and researchers could compare every patient data source with characteristics and longitudinal trend in the Report Service. This method allows dynamically generating a clinical data mart, and reduces the computation overhead through the reuse of the same patient list. This design can inspire researchers and allow them to focus on the research design rather than data processing.

The other systems have not considered a high reusability infrastructure for evaluation the clinical effectiveness and safety in multiple sub-cohorts. In NCSS, with our newly proposed architecture, Stage 3 Cohort Tree Analysis, it has powerful features for statistical inference, statistical adjustment for confounding, data pre-processing, data visualization and generating risk effect estimates. This integrated solution allows dynamically generating multiple analysis-ready datasets in Data Mart, and reduces the computation overhead through the reuse of the similar research design. This mechanism can inspire researchers and support more efficient outcome validation rather than data processing.

In summary, by building up an integrated survival analysis workflow to achieve the following targets, this study solves the following bottlenecks in constructing a timely post-marketing surveillance system. First, the accessibility, we make the tool as straightforward as possible and it can reduce the learning threshold of clinical researches. Second, the efficiency, the NCSS is an online web application that can quickly respond in each step automatically to process statistical analysis. Third, outcomes assessed in inferential analyses, the NCSS supports researcher to identify medical conditions defined as outcomes of interest in inferential

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analyses and their respective code lists and algorithm criteria. The NCSS will not only help researchers in the field of outcome research to analyze their data in depth but also will potentially facilitate the standardization of survival analysis at a medical center in Taiwan.

5.3 Limitations

Some limitations should be addressed in this study. First, we only generated the NCSS system at only one medical center in Taiwan. For acute diseases, patients may be treated in a nearby hospital. If these acute diseases happen to be rare events, the NCSS would not be able to detect the risk signal. However, the current study results may likely be generalized to other medical centers with features similar to our medical center. Second, the use of diagnosis codes to identify the study cohort relied on the quality of coding in the hospital. A previous study [80] demonstrates that the medical center typically had better coding quality compared with the district hospital, and all the hospital must pass the same level of accreditation with the National Health Insurance Administration in Taiwan. Third, the schema of electronic medical records is different, so if we want to get the same results that mapping to the same common data model is necessary. Fourth, the current NCSS only automatically extracts structure data in EMRs. Deep learning offers many opportunities for natural language processing and image classification [81, 82]. In fact, some quality measures that use only unstructured data from the EMRs are relatively difficult to automate. Some unstructured data, such as ultrasound reports or X-ray reports, still currently free text. Therefore, most clinical studies mainly use structured data for research. Future work may consider combining unstructured data for clinical research.

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5.4 Future Work

The identification of the problem is the first step to solve and improve the clinical outcome of the patient. By applying computerized patient identification derived from the NCSS, we can create the infrastructure of an informatics system at NTUH. Furthermore, we can provide decision support in daily practice, thereby making the benefit of evidence-based medicine a reality. In fact, we believe that the best way to promote medical care is to provide relevant evidence to assist doctors in their decision making process during their clinical daily practice. For example, an evaluation of the longitudinal trends of health care utilization can help create a baseline, track progress over time, and generate real-world evidence. Besides providing clinical support for physicians, the next step will be providing integrated real-time, interactive, and personalized support to individual patients [13, 83]. This will be focused on in a future study. Finally, we strongly advocate developing a consistent strategy, as well as celebrating success and continuously sharing different experiences. The continual reduction in the gap between evidence and practice is an ongoing journey, and not an end that can simply be reached shortly after the NCSS implemented.

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Chapter 6. Conclusion

Until 2018, the NCSS has been well-constructed and continuously improving. Our teams consist of individuals in multidisciplinary specialties such as a clinical doctor, pharmacist, biomedical engineer, epidemiologist. These research teams regularly hold monthly meetings to discuss the related problems of application of the NCSS. In the period between 2015 and 2018, each research team created dozens of cohorts. Several research teams have used the NCSS to enhance the research process based on their relevant clinical needs. Moreover, a large sum of meaningful feedback has been received for not only the problem related to using the NCSS but also recommendations for improving the NCSS. Finally, we accomplished the assistant resources such as the user handbook and online video tutorials. This helps the research team readily assess the NCSS. These application experiences and associated feedback helps improve the NCSS efficiency and quality of clinical research at NTUH.

An evaluation of the longitudinal trends of health care utilization can help create the baseline, track progress over time, and generate real-world evidence. The NCSS can serve the critical role of forming associations between evidence derived from clinical trials and the real world in a rapid fashion, and can be a support system for researchers who wish to confirm certain clinical issues, as well as for those requiring a computerized system to complete their studies.

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APPENDIX

Appendix A. Abbreviations

NCSS: National Taiwan University Hospital Clinical Surveillance System

NTUH: National Taiwan University Hospital

STRIDE: Stanford Translational Research Integrated Database Environment

REDCap: Research Electronic Data Capture

OHDSI: The Observational Health Data Sciences and Informatics

i2b2: Integrating Biology & the Bedside

AOMs: Anti-Osteoporosis Medications

DW: Data Warehouse

IMDB: Integrated Medical Database

ETL: Extraction, Transformation, and Loading

REC: Research Institutional Ethics Committee

ICD: International Classification of Diseases

ATC: Anatomical Therapeutic Chemical

BMI: Body Mass Index

EHR: Electronic Healthcare Record

VKA: Vitamin K Antagonists

NOACs: Non-vitamin K Antagonist Oral Anticoagulants

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AF: Atrial fibrillation

HR: Hazard Ratio

TIA: Transient Ischemic Attack

VTE: Venous Thromboembolism

ICH: Intracranial Hemorrhage

GI: Gastro-intestinal

ITT: Intention to Treat

AT: As Treated

SMD: Standardized Mean Differences

FDA: Food and Drug Administration

AsPEN: Asian Pharmaco-epidemiology Network

PSSA: Prescription Sequence Symmetry Analysis

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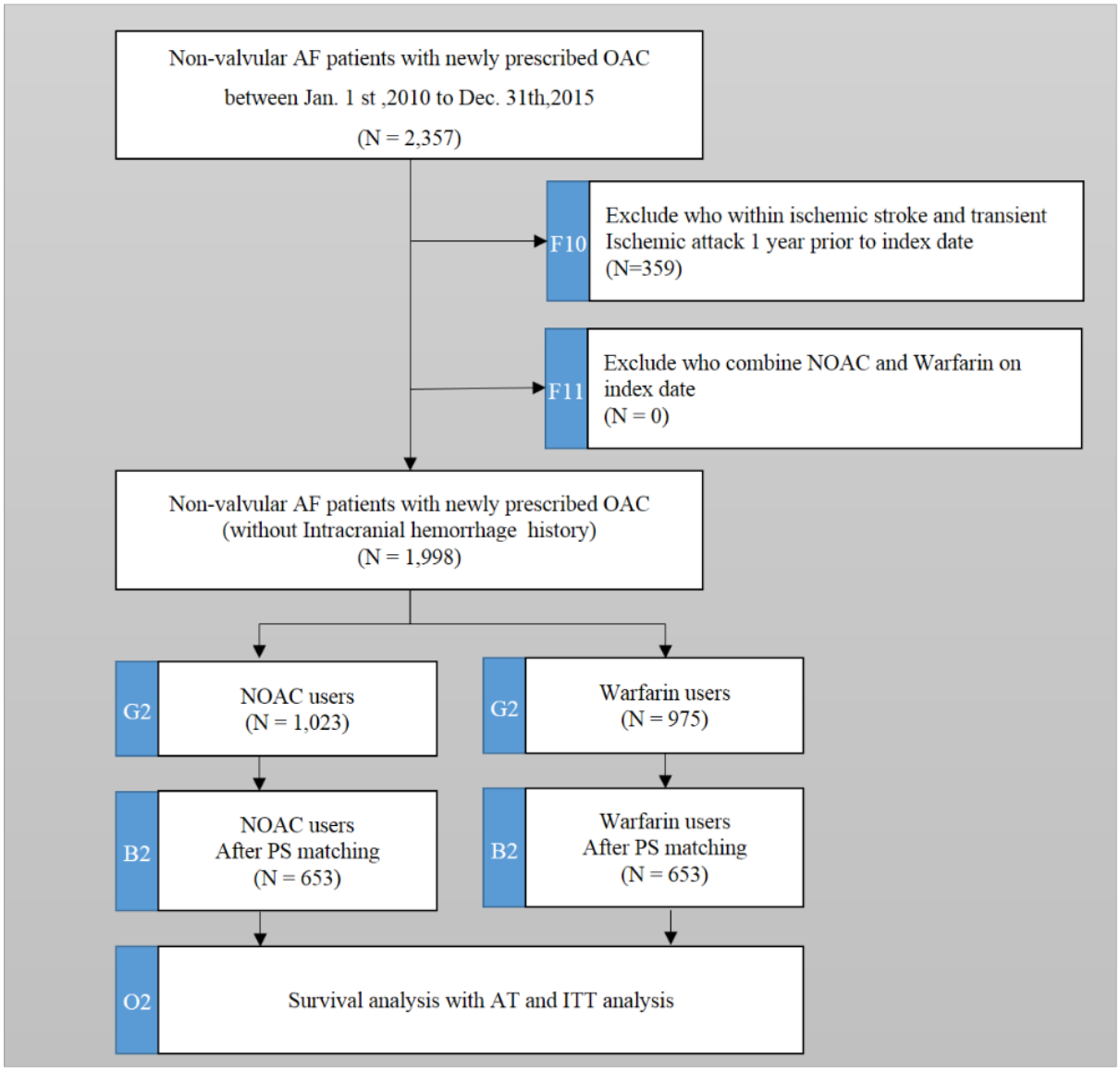
Appendix B. The details of sub-cohorts

1. The sub-cohort of transient ischemic attack

(a) The study flow of sub-cohort of transient ischemic attack.



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(b) Basic characteristics of the sub-cohort of transient ischemic attack before Propensity Score Matching.

Before Propensity Score Matching

	NOAC	Warfarin	SMD
n	1023	975	
ARBs/ACEIs = 1 (%)	481 (47.0)	378 (38.8)	0.167
Acute myocardial infarction = 1 (%)	24 (2.3)	12 (1.2)	0.084
Age 65-69 = 1 (%)	166 (16.2)	138 (14.2)	0.058
Age 70-74 = 1 (%)	197 (19.3)	112 (11.5)	0.217
Age 75-79 = 1 (%)	208 (20.3)	123 (12.6)	0.209
Age <65 = 1 (%)	133 (13.0)	418 (42.9)	0.706
Age >=80 = 1 (%)	319 (31.2)	184 (18.9)	0.287
Antiplatelet drugs = 1 (%)	524 (51.2)	374 (38.4)	0.261
Coagulation deficiency = 1 (%)	1 (0.1)	2 (0.2)	0.028
Diabetes = 1 (%)	236 (23.1)	168 (17.2)	0.146
Digoxin = 1 (%)	124 (12.1)	131 (13.4)	0.039
Dihydropyridine calcium channel blockers = 1 (%)	356 (34.8)	257 (26.4)	0.184
GI bleeding = 1 (%)	25 (2.4)	23 (2.4)	0.006
Gender = 1 (%)	427 (41.7)	378 (38.8)	0.061
H2 receptor antagonist = 1 (%)	105 (10.3)	87 (8.9)	0.046
Heart failure = 1 (%)	176 (17.2)	162 (16.6)	0.016
Hypertension = 1 (%)	514 (50.2)	406 (41.6)	0.173
Intracranial hemorrhage = 1 (%)	7 (0.7)	4 (0.4)	0.037
Liver disease = 1 (%)	34 (3.3)	45 (4.6)	0.066
NSAIDs = 1 (%)	150 (14.7)	136 (13.9)	0.020
Non-dihydropyridine calcium channel blockers = 1 (%)	147 (14.4)	133 (13.6)	0.021
Other antacids = 1 (%)	275 (26.9)	273 (28.0)	0.025
Peptic ulcer disease = 1 (%)	54 (5.3)	43 (4.4)	0.040
Peripheral vascular disease = 1 (%)	16 (1.6)	17 (1.7)	0.014
Proton-pump inhibitor = 1 (%)	98 (9.6)	120 (12.3)	0.087
Renal disease = 1 (%)	25 (2.4)	69 (7.1)	0.219
Statins = 1 (%)	240 (23.5)	160 (16.4)	0.177
Venous Thromboembolism = 1 (%)	9 (0.9)	12 (1.2)	0.034
anti-diabetes drugs = 1 (%)	191 (18.7)	155 (15.9)	0.073
antiarrhythmic drugs = 1 (%)	388 (37.9)	393 (40.3)	0.049
beta-blockering agents = 1 (%)	449 (43.9)	431 (44.2)	0.006

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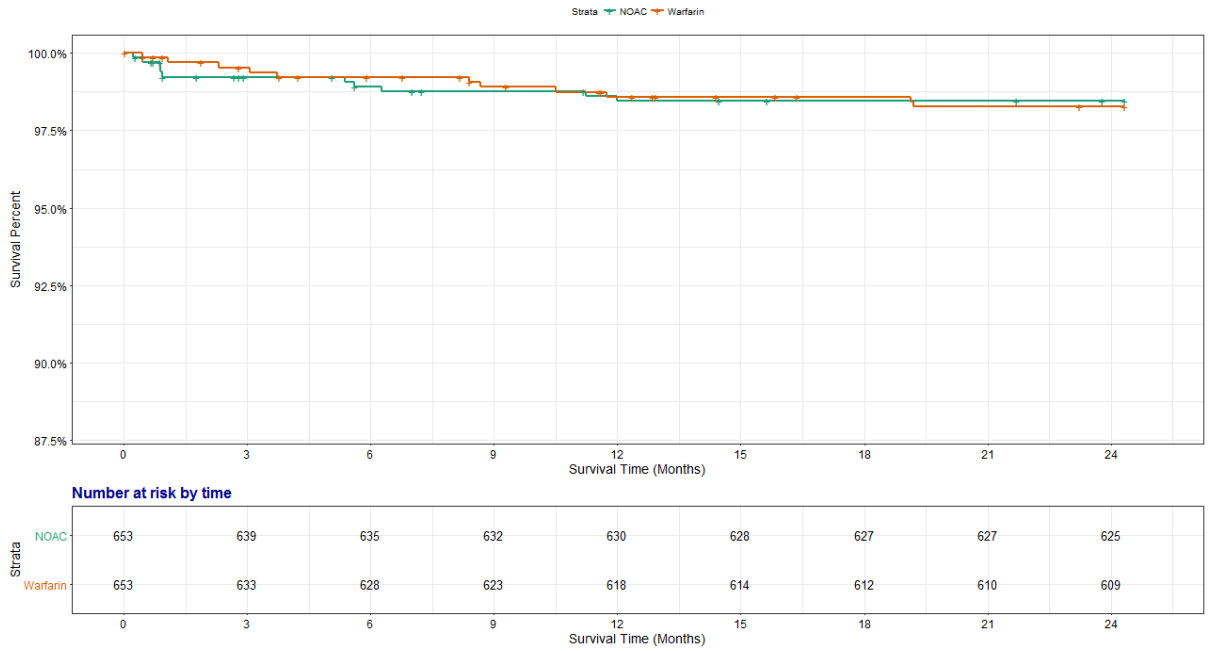
(c) Basic characteristics of the sub-cohort of transient ischemic attack after Propensity Score Matching.

After Propensity Score Matching

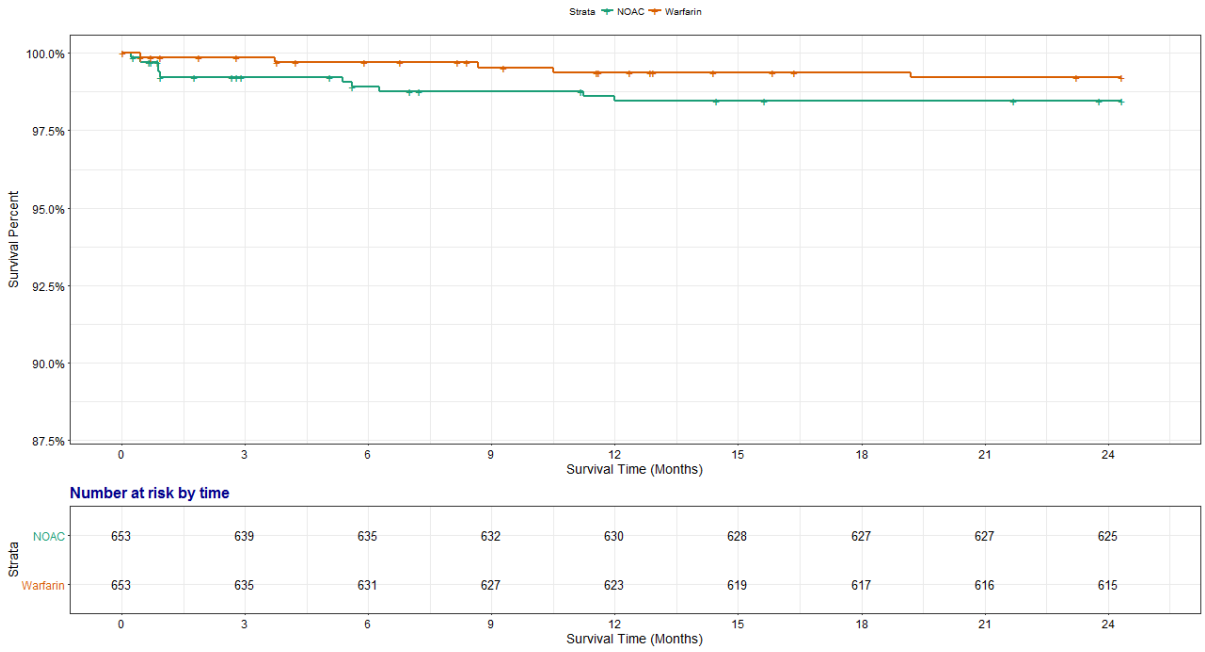
	NOAC	Warfarin	SMD
n	653	653	
ARBs/ACEIs = 1 (%)	251 (38.4)	278 (42.6)	0.084
Acute myocardial infarction = 1 (%)	10 (1.5)	11 (1.7)	0.012
Age 65-69 = 1 (%)	122 (18.7)	127 (19.4)	0.019
Age 70-74 = 1 (%)	113 (17.3)	106 (16.2)	0.029
Age 75-79 = 1 (%)	113 (17.3)	115 (17.6)	0.008
Age <65 = 1 (%)	132 (20.2)	136 (20.8)	0.015
Age >=80 = 1 (%)	173 (26.5)	169 (25.9)	0.014
Antiplatelet drugs = 1 (%)	260 (39.8)	274 (42.0)	0.044
Coagulation deficiency = 1 (%)	1 (0.2)	1 (0.2)	<0.001
Diabetes = 1 (%)	132 (20.2)	134 (20.5)	0.008
Digoxin = 1 (%)	86 (13.2)	92 (14.1)	0.027
Dihydropyridine calcium channel blockers = 1 (%)	189 (28.9)	198 (30.3)	0.030
GI bleeding = 1 (%)	19 (2.9)	13 (2.0)	0.059
Gender = 1 (%)	281 (43.0)	281 (43.0)	<0.001
H2 receptor antagonist = 1 (%)	62 (9.5)	62 (9.5)	<0.001
Heart failure = 1 (%)	108 (16.5)	115 (17.6)	0.028
Hypertension = 1 (%)	289 (44.3)	302 (46.2)	0.040
Intracranial hemorrhage = 1 (%)	4 (0.6)	4 (0.6)	<0.001
Liver disease = 1 (%)	26 (4.0)	23 (3.5)	0.024
NSAIDs = 1 (%)	103 (15.8)	97 (14.9)	0.026
Non-dihydropyridine calcium channel blockers = 1 (%)	82 (12.6)	93 (14.2)	0.049
Other antacids = 1 (%)	208 (31.9)	193 (29.6)	0.050
Peptic ulcer disease = 1 (%)	33 (5.1)	32 (4.9)	0.007
Peripheral vascular disease = 1 (%)	11 (1.7)	14 (2.1)	0.034
Proton-pump inhibitor = 1 (%)	79 (12.1)	78 (11.9)	0.005
Renal disease = 1 (%)	24 (3.7)	30 (4.6)	0.046
Statins = 1 (%)	113 (17.3)	121 (18.5)	0.032
Venous Thromboembolism = 1 (%)	5 (0.8)	8 (1.2)	0.046
anti-diabetes drugs = 1 (%)	110 (16.8)	117 (17.9)	0.028
antiarrhythmic drugs = 1 (%)	245 (37.5)	248 (38.0)	0.009
beta-blockering agents = 1 (%)	274 (42.0)	276 (42.3)	0.006

doi:10.6342/NTU201900301

(d) Kaplan–Meier Survival Plots of transient ischemic attack with ITT analysis



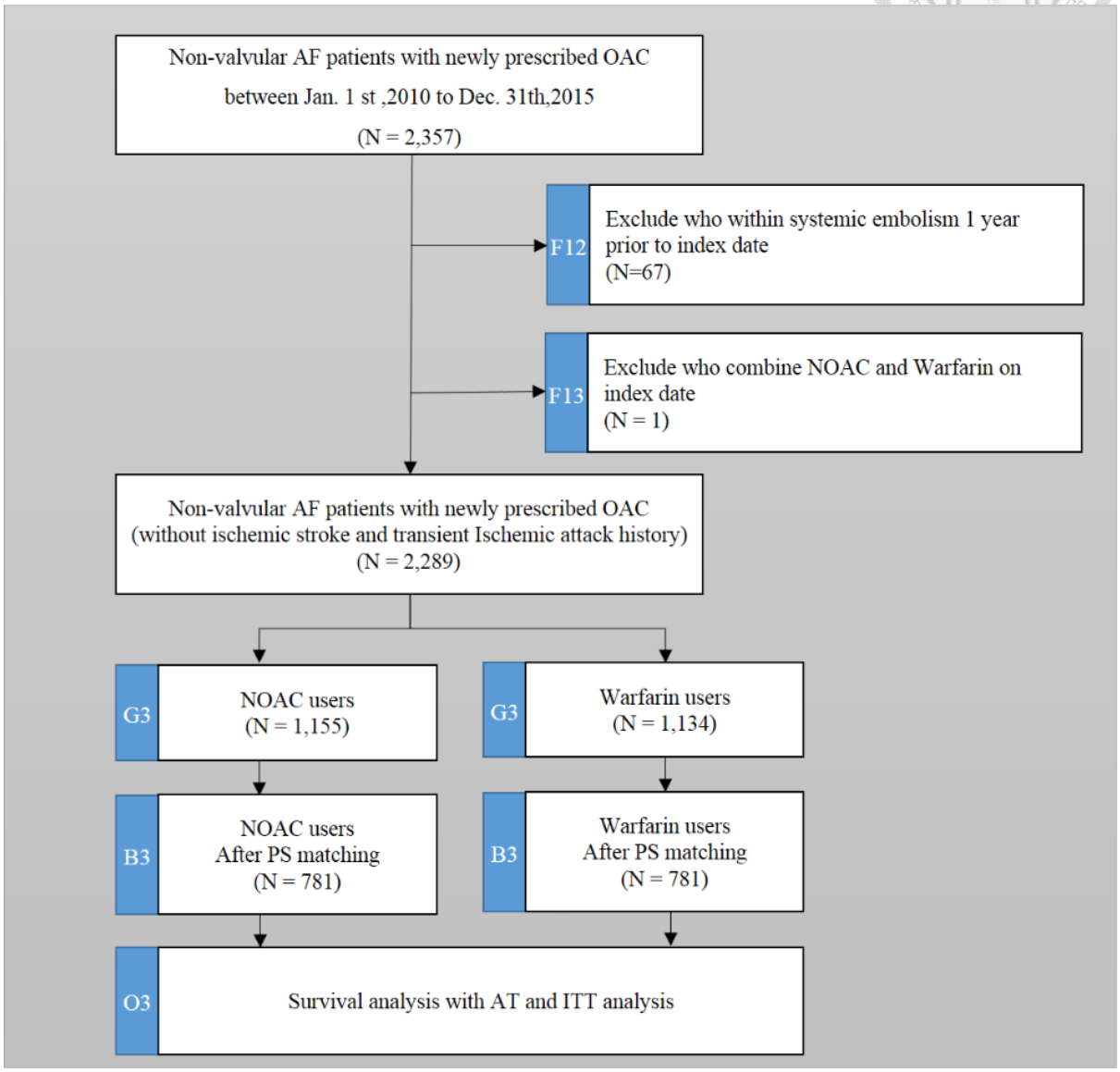
(e) Kaplan–Meier Survival Plots of transient ischemic attack with AT analysis



doi:10.6342/NTU201900301

2. The sub-cohort of systemic embolism

(a) The study flow of sub-cohort of systemic embolism.



doi:10.6342/NTU201900301

(b) Basic characteristics of the sub-cohort of systemic embolism before Propensity Score Matching.

Before Propensity Score Matching

	NOAC	Warfarin	SMD
n	1155	1134	
ARBs/ACEIs = 1 (%)	540 (46.8)	449 (39.6)	0.145
Acute myocardial infarction = 1 (%)	23 (2.0)	13 (1.1)	0.068
Age 65-69 = 1 (%)	187 (16.2)	161 (14.2)	0.056
Age 70-74 = 1 (%)	223 (19.3)	144 (12.7)	0.181
Age 75-79 = 1 (%)	230 (19.9)	146 (12.9)	0.191
Age <65 = 1 (%)	162 (14.0)	468 (41.3)	0.640
Age >=80 = 1 (%)	353 (30.6)	215 (19.0)	0.271
Antiplatelet drugs = 1 (%)	615 (53.2)	477 (42.1)	0.225
Coagulation deficiency = 1 (%)	1 (0.1)	2 (0.2)	0.025
Diabetes = 1 (%)	253 (21.9)	201 (17.7)	0.105
Digoxin = 1 (%)	137 (11.9)	169 (14.9)	0.089
Dihydropyridine calcium channel blockers = 1 (%)	414 (35.8)	328 (28.9)	0.148
GI bleeding = 1 (%)	28 (2.4)	28 (2.5)	0.003
Gender = 1 (%)	495 (42.9)	441 (38.9)	0.081
H2 receptor antagonist = 1 (%)	130 (11.3)	111 (9.8)	0.048
Heart failure = 1 (%)	184 (15.9)	179 (15.8)	0.004
Hypertension = 1 (%)	561 (48.6)	468 (41.3)	0.147
Intracranial hemorrhage = 1 (%)	9 (0.8)	7 (0.6)	0.019
Ischemic stroke = 1 (%)	97 (8.4)	101 (8.9)	0.018
Liver disease = 1 (%)	39 (3.4)	48 (4.2)	0.045
NSAIDs = 1 (%)	192 (16.6)	173 (15.3)	0.037
Non-dihydropyridine calcium channel blockers = 1 (%)	188 (16.3)	197 (17.4)	0.029
Other antacids = 1 (%)	352 (30.5)	391 (34.5)	0.086
Peptic ulcer disease = 1 (%)	56 (4.8)	46 (4.1)	0.038
Peripheral vascular disease = 1 (%)	30 (2.6)	31 (2.7)	0.008
Proton-pump inhibitor = 1 (%)	172 (14.9)	212 (18.7)	0.102
Renal disease = 1 (%)	27 (2.3)	71 (6.3)	0.194
Statins = 1 (%)	288 (24.9)	218 (19.2)	0.138
Transient ischemic attack = 1 (%)	15 (1.3)	22 (1.9)	0.051
Venous Thromboembolism = 1 (%)	11 (1.0)	11 (1.0)	0.002
anti-diabetes drugs = 1 (%)	216 (18.7)	200 (17.6)	0.028
antiarrhythmic drugs = 1 (%)	423 (36.6)	454 (40.0)	0.070
beta-blockering agents = 1 (%)	517 (44.8)	519 (45.8)	0.020

doi:10.6342/NTU201900301

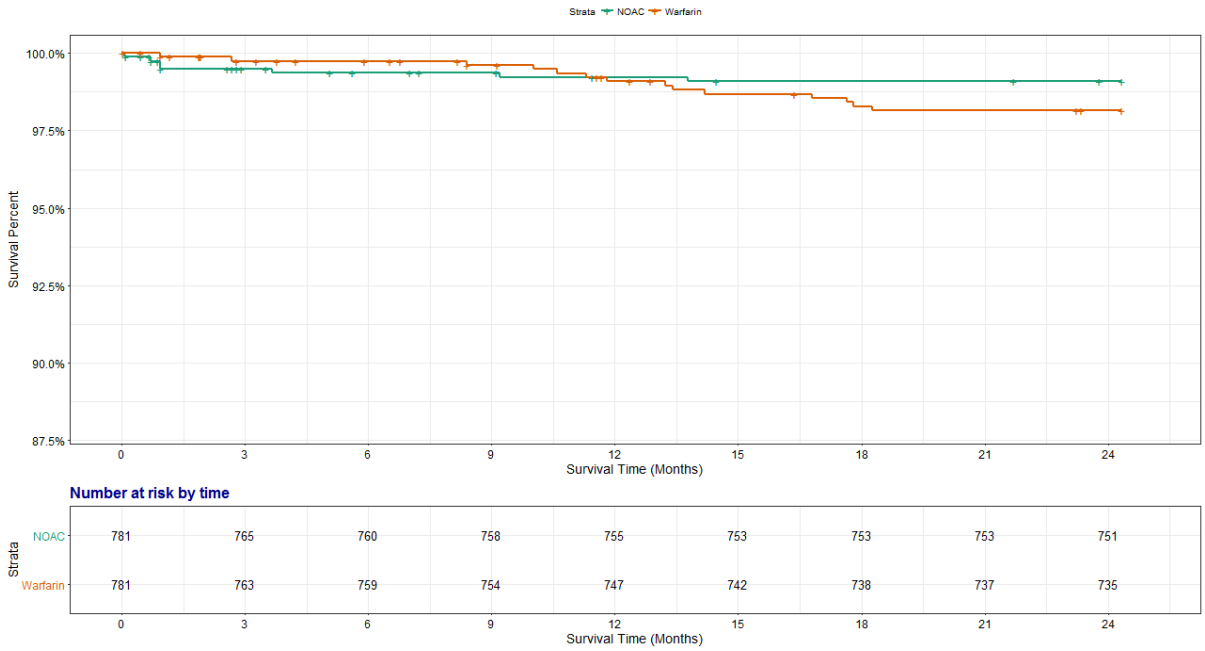
(c) Basic characteristics of the sub-cohort of systemic embolism after Propensity Score Matching.

After Propensity Score Matching

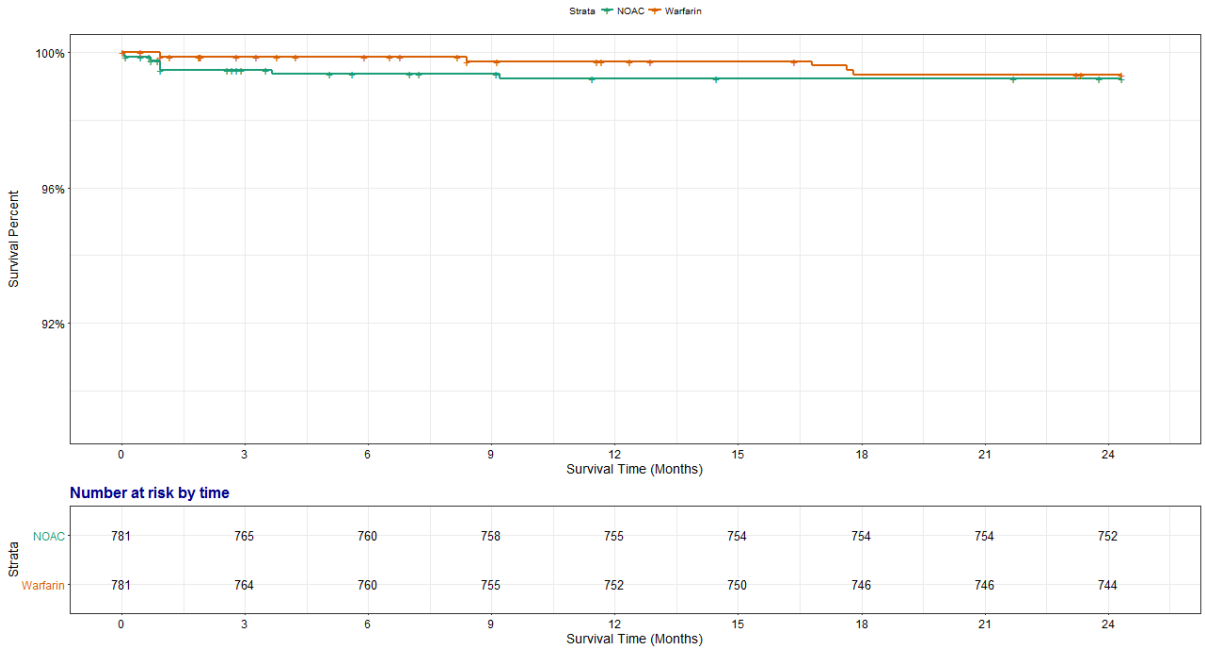
	NOAC	Warfarin	SMD
n	781	781	
ARBs/ACEIs = 1 (%)	300 (38.4)	327 (41.9)	0.071
Acute myocardial infarction = 1 (%)	12 (1.5)	13 (1.7)	0.010
Age 65-69 = 1 (%)	152 (19.5)	147 (18.8)	0.016
Age 70-74 = 1 (%)	136 (17.4)	134 (17.2)	0.007
Age 75-79 = 1 (%)	131 (16.8)	130 (16.6)	0.003
Age <65 = 1 (%)	161 (20.6)	174 (22.3)	0.041
Age >=80 = 1 (%)	201 (25.7)	196 (25.1)	0.015
Antiplatelet drugs = 1 (%)	335 (42.9)	356 (45.6)	0.054
Coagulation deficiency = 1 (%)	1 (0.1)	1 (0.1)	<0.001
Diabetes = 1 (%)	140 (17.9)	148 (19.0)	0.026
Digoxin = 1 (%)	92 (11.8)	110 (14.1)	0.069
Dihydropyridine calcium channel blockers = 1 (%)	223 (28.6)	252 (32.3)	0.081
GI bleeding = 1 (%)	18 (2.3)	15 (1.9)	0.027
Gender = 1 (%)	317 (40.6)	328 (42.0)	0.029
H2 receptor antagonist = 1 (%)	78 (10.0)	84 (10.8)	0.025
Heart failure = 1 (%)	122 (15.6)	119 (15.2)	0.011
Hypertension = 1 (%)	334 (42.8)	349 (44.7)	0.039
Intracranial hemorrhage = 1 (%)	4 (0.5)	7 (0.9)	0.046
Ischemic stroke = 1 (%)	72 (9.2)	75 (9.6)	0.013
Liver disease = 1 (%)	27 (3.5)	21 (2.7)	0.045
NSAIDs = 1 (%)	127 (16.3)	131 (16.8)	0.014
Non-dihydropyridine calcium channel blockers = 1 (%)	133 (17.0)	137 (17.5)	0.014
Other antacids = 1 (%)	282 (36.1)	278 (35.6)	0.011
Peptic ulcer disease = 1 (%)	34 (4.4)	42 (5.4)	0.048
Peripheral vascular disease = 1 (%)	21 (2.7)	23 (2.9)	0.015
Proton-pump inhibitor = 1 (%)	137 (17.5)	147 (18.8)	0.033
Renal disease = 1 (%)	26 (3.3)	23 (2.9)	0.022
Statins = 1 (%)	159 (20.4)	166 (21.3)	0.022
Transient ischemic attack = 1 (%)	14 (1.8)	14 (1.8)	<0.001
Venous Thromboembolism = 1 (%)	6 (0.8)	10 (1.3)	0.051
anti-diabetes drugs = 1 (%)	130 (16.6)	139 (17.8)	0.031
antiarrhythmic drugs = 1 (%)	277 (35.5)	292 (37.4)	0.040
beta-blockering agents = 1 (%)	346 (44.3)	342 (43.8)	0.010

doi:10.6342/NTU201900301

(d) Kaplan–Meier Survival Plots of systemic embolism with ITT analysis



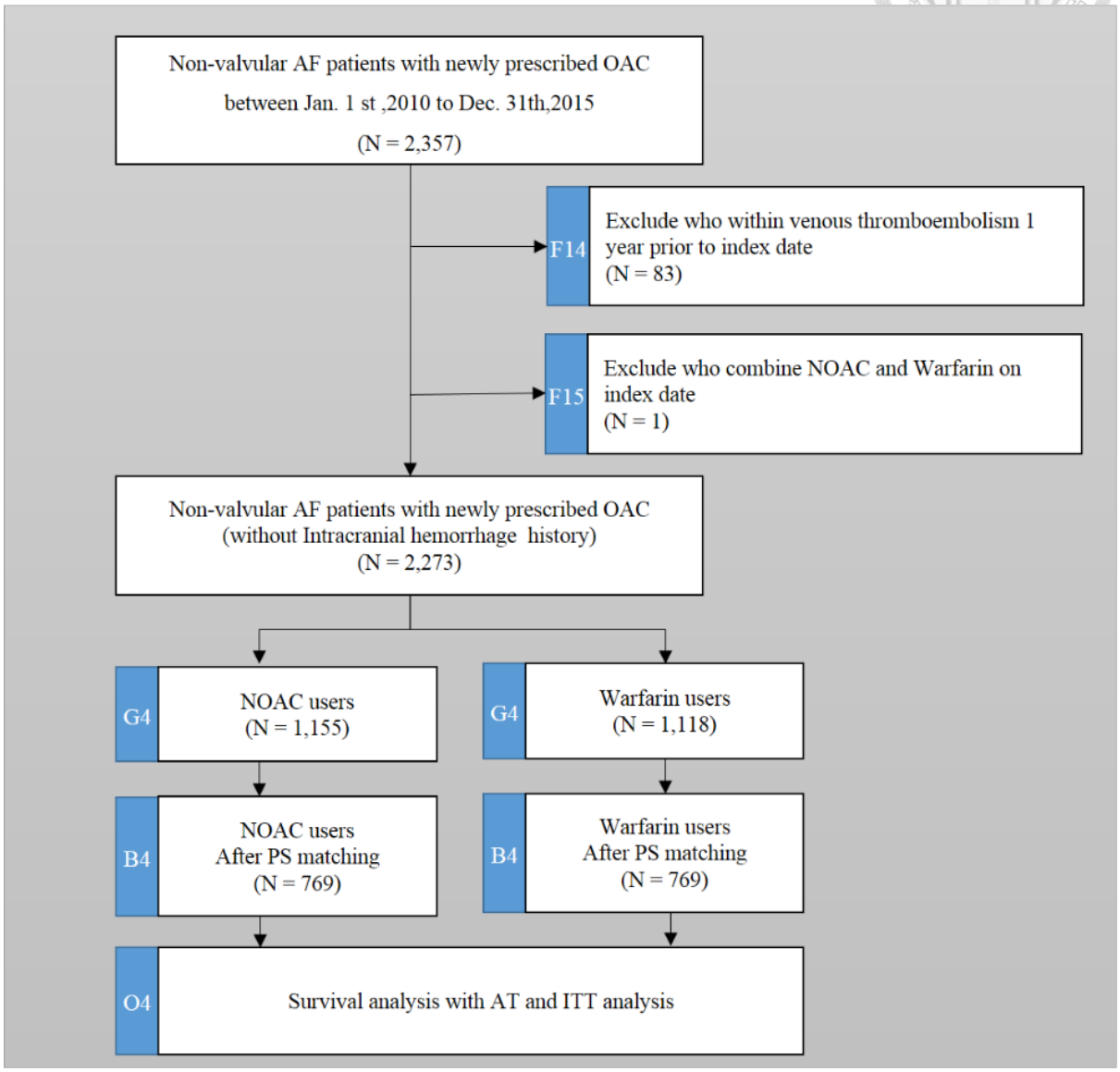
(e) Kaplan–Meier Survival Plots of systemic embolism with AT analysis



doi:10.6342/NTU201900301

3. The sub-cohort of venous thromboembolism.

(a) The study flow of sub-cohort of venous thromboembolism.



doi:10.6342/NTU201900301

(b) Basic characteristics of the sub-cohort of venous thromboembolism before Propensity Score Matching.

Before Propensity Score Matching

	NOAC	Warfarin	SMD
n	1155	1118	
ARBs/ACEIs = 1 (%)	544 (47.1)	452 (40.4)	0.135
Acute myocardial infarction = 1 (%)	26 (2.3)	14 (1.3)	0.076
Age 65-69 = 1 (%)	185 (16.0)	161 (14.4)	0.045
Age 70-74 = 1 (%)	225 (19.5)	139 (12.4)	0.193
Age 75-79 = 1 (%)	218 (18.9)	139 (12.4)	0.178
Age <65 = 1 (%)	160 (13.9)	464 (41.5)	0.650
Age >=80 = 1 (%)	367 (31.8)	215 (19.2)	0.291
Antiplatelet drugs = 1 (%)	619 (53.6)	473 (42.3)	0.227
Coagulation deficiency = 1 (%)	1 (0.1)	2 (0.2)	0.025
Diabetes = 1 (%)	263 (22.8)	204 (18.2)	0.112
Digoxin = 1 (%)	134 (11.6)	164 (14.7)	0.091
Dihydropyridine calcium channel blockers = 1 (%)	425 (36.8)	335 (30.0)	0.145
GI bleeding = 1 (%)	27 (2.3)	27 (2.4)	0.005
Gender = 1 (%)	490 (42.4)	429 (38.4)	0.083
H2 receptor antagonist = 1 (%)	137 (11.9)	112 (10.0)	0.059
Heart failure = 1 (%)	185 (16.0)	175 (15.7)	0.010
Hypertension = 1 (%)	568 (49.2)	464 (41.5)	0.155
Intracranial hemorrhage = 1 (%)	11 (1.0)	6 (0.5)	0.048
Ischemic stroke = 1 (%)	92 (8.0)	99 (8.9)	0.032
Liver disease = 1 (%)	39 (3.4)	43 (3.8)	0.025
NSAIDs = 1 (%)	187 (16.2)	171 (15.3)	0.025
Non-dihydropyridine calcium channel blockers = 1 (%)	187 (16.2)	191 (17.1)	0.024
Other antacids = 1 (%)	355 (30.7)	379 (33.9)	0.068
Peptic ulcer disease = 1 (%)	59 (5.1)	44 (3.9)	0.056
Peripheral vascular disease = 1 (%)	31 (2.7)	35 (3.1)	0.027
Proton-pump inhibitor = 1 (%)	172 (14.9)	205 (18.3)	0.093
Renal disease = 1 (%)	25 (2.2)	72 (6.4)	0.212
Statins = 1 (%)	299 (25.9)	218 (19.5)	0.153
anti-diabetes drugs = 1 (%)	227 (19.7)	203 (18.2)	0.038
antiarrhythmic drugs = 1 (%)	425 (36.8)	445 (39.8)	0.062
beta-blockering agents = 1 (%)	521 (45.1)	517 (46.2)	0.023

doi:10.6342/NTU201900301

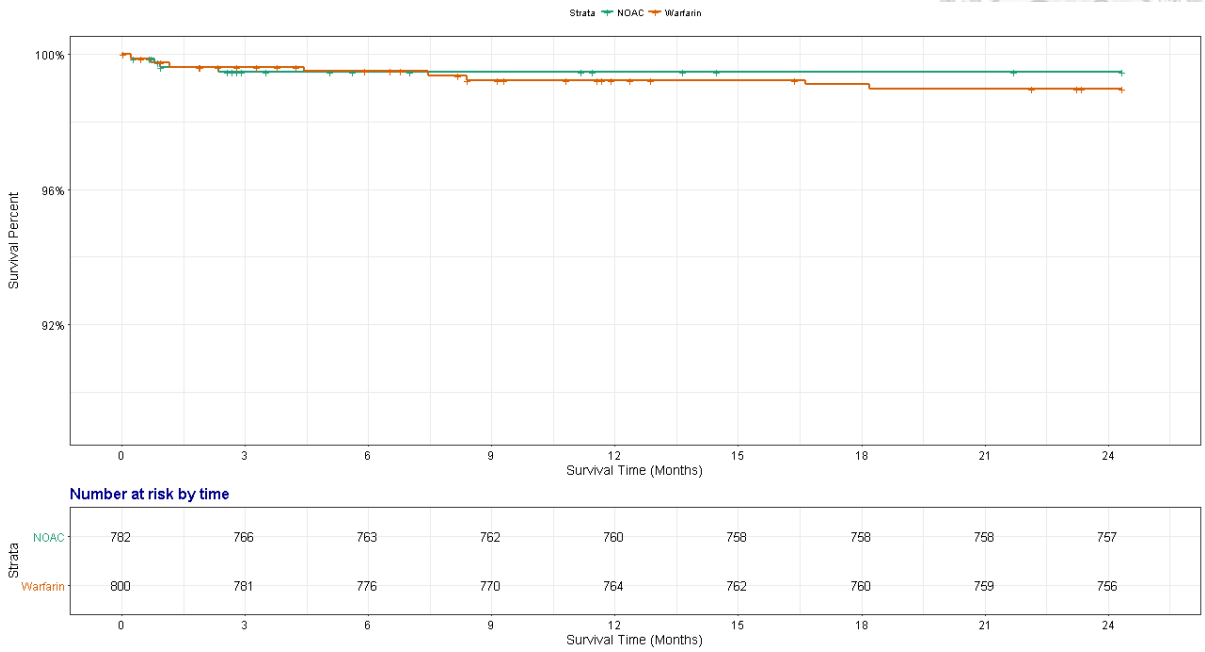
(c) Basic characteristics of the sub-cohort of venous thromboembolism after Propensity Score Matching.

After Propensity Score Matching

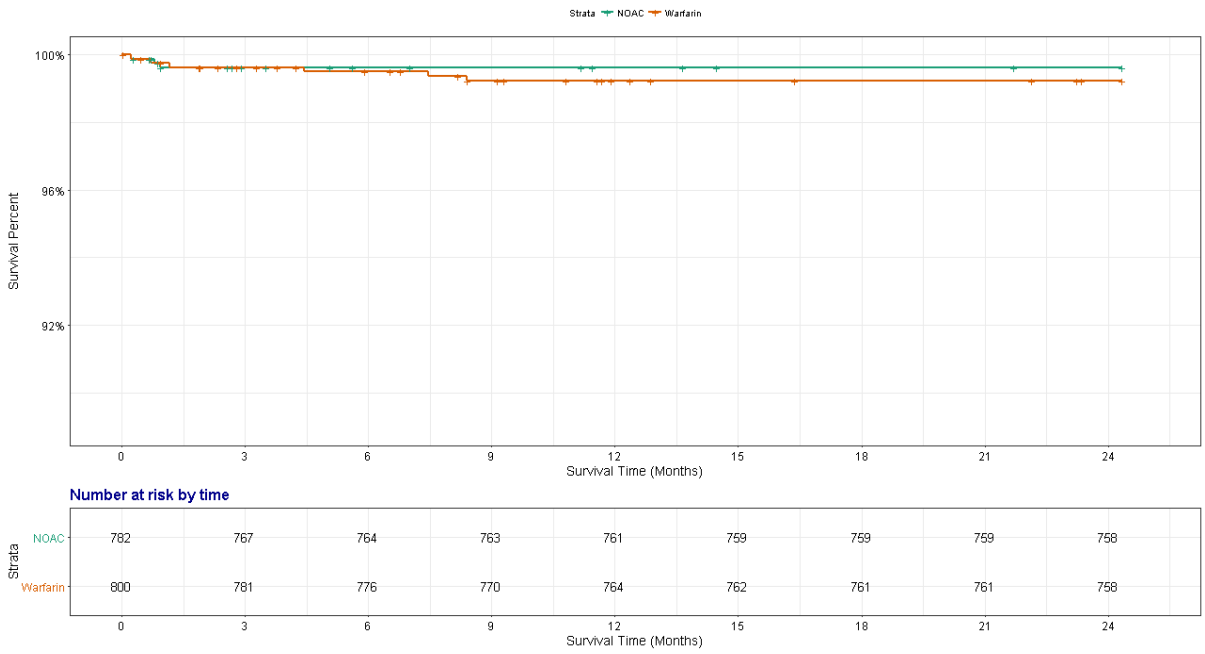
	NOAC	Warfarin	SMD
n	769	769	
ARBs/ACEIs = 1 (%)	310 (40.3)	327 (42.5)	0.045
Acute myocardial infarction = 1 (%)	11 (1.4)	13 (1.7)	0.021
Age 65-69 = 1 (%)	145 (18.9)	148 (19.2)	0.010
Age 70-74 = 1 (%)	133 (17.3)	129 (16.8)	0.014
Age 75-79 = 1 (%)	129 (16.8)	124 (16.1)	0.018
Age <65 = 1 (%)	160 (20.8)	171 (22.2)	0.035
Age >=80 = 1 (%)	202 (26.3)	197 (25.6)	0.015
Antiplatelet drugs = 1 (%)	324 (42.1)	349 (45.4)	0.066
Coagulation deficiency = 1 (%)	1 (0.1)	0 (0.0)	0.051
Diabetes = 1 (%)	141 (18.3)	147 (19.1)	0.020
Digoxin = 1 (%)	94 (12.2)	113 (14.7)	0.072
Dihydropyridine calcium channel blockers = 1 (%)	242 (31.5)	252 (32.8)	0.028
GI bleeding = 1 (%)	20 (2.6)	14 (1.8)	0.053
Gender = 1 (%)	324 (42.1)	322 (41.9)	0.005
H2 receptor antagonist = 1 (%)	78 (10.1)	87 (11.3)	0.038
Heart failure = 1 (%)	118 (15.3)	122 (15.9)	0.014
Hypertension = 1 (%)	333 (43.3)	345 (44.9)	0.031
Intracranial hemorrhage = 1 (%)	5 (0.7)	5 (0.7)	<0.001
Ischemic stroke = 1 (%)	63 (8.2)	73 (9.5)	0.046
Liver disease = 1 (%)	23 (3.0)	19 (2.5)	0.032
NSAIDs = 1 (%)	129 (16.8)	125 (16.3)	0.014
Non-dihydropyridine calcium channel blockers = 1 (%)	119 (15.5)	131 (17.0)	0.042
Other antacids = 1 (%)	272 (35.4)	274 (35.6)	0.005
Peptic ulcer disease = 1 (%)	30 (3.9)	40 (5.2)	0.062
Peripheral vascular disease = 1 (%)	22 (2.9)	25 (3.3)	0.023
Proton-pump inhibitor = 1 (%)	136 (17.7)	141 (18.3)	0.017
Renal disease = 1 (%)	25 (3.3)	23 (3.0)	0.015
Statins = 1 (%)	149 (19.4)	167 (21.7)	0.058
anti-diabetes drugs = 1 (%)	130 (16.9)	139 (18.1)	0.031
antiarrhythmic drugs = 1 (%)	282 (36.7)	287 (37.3)	0.013
beta-blockering agents = 1 (%)	335 (43.6)	339 (44.1)	0.010

doi:10.6342/NTU201900301

(d) Kaplan–Meier Survival Plots of venous thromboembolism with ITT analysis.



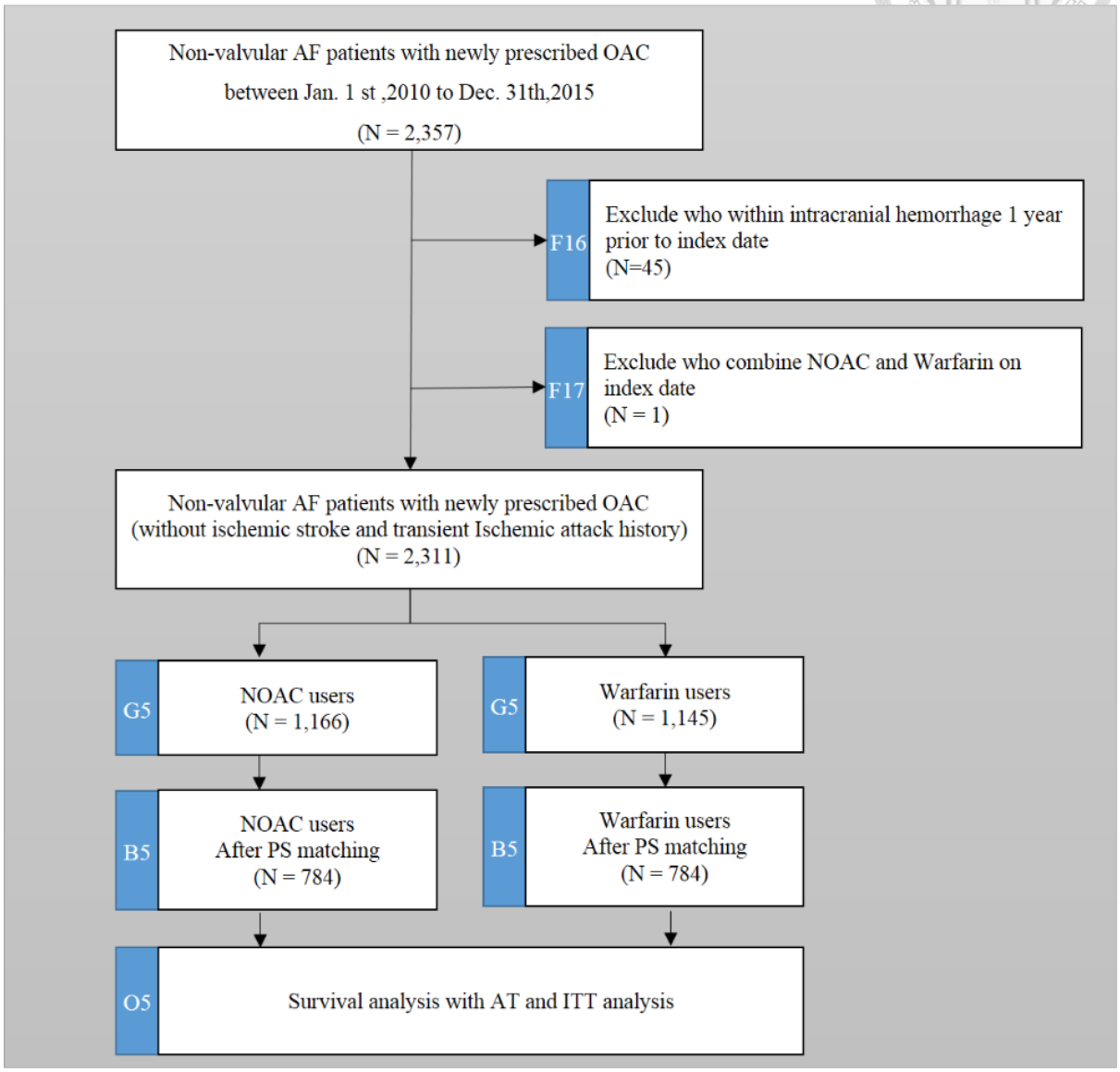
(e) Kaplan–Meier Survival Plots of venous thromboembolism with AT analysis.



doi:10.6342/NTU201900301

4. The sub-cohort of intracranial hemorrhage.

(a) The study flow of sub-cohort of intracranial hemorrhage.



doi:10.6342/NTU201900301

(b) Basic characteristics of the sub-cohort of intracranial hemorrhage before Propensity Score Matching.

Before Propensity Score Matching

	NOAC	Warfarin	SMD
n	1166	1145	
ARBs/ACEIs = 1 (%)	548 (47.0)	455 (39.7)	0.147
Acute myocardial infarction = 1 (%)	25 (2.1)	14 (1.2)	0.072
Age 65-69 = 1 (%)	188 (16.1)	160 (14.0)	0.060
Age 70-74 = 1 (%)	222 (19.0)	144 (12.6)	0.178
Age 75-79 = 1 (%)	231 (19.8)	148 (12.9)	0.187
Age <65 = 1 (%)	159 (13.6)	470 (41.0)	0.646
Age >=80 = 1 (%)	366 (31.4)	223 (19.5)	0.276
Antiplatelet drugs = 1 (%)	630 (54.0)	494 (43.1)	0.219
Coagulation deficiency = 1 (%)	1 (0.1)	3 (0.3)	0.042
Diabetes = 1 (%)	265 (22.7)	206 (18.0)	0.118
Digoxin = 1 (%)	136 (11.7)	168 (14.7)	0.089
Dihydropyridine calcium channel blockers = 1 (%)	419 (35.9)	335 (29.3)	0.143
GI bleeding = 1 (%)	29 (2.5)	29 (2.5)	0.003
Gender = 1 (%)	497 (42.6)	444 (38.8)	0.078
H2 receptor antagonist = 1 (%)	133 (11.4)	115 (10.0)	0.044
Heart failure = 1 (%)	188 (16.1)	183 (16.0)	0.004
Hypertension = 1 (%)	575 (49.3)	477 (41.7)	0.154
Ischemic stroke = 1 (%)	94 (8.1)	90 (7.9)	0.007
Liver disease = 1 (%)	38 (3.3)	50 (4.4)	0.058
NSAIDs = 1 (%)	191 (16.4)	176 (15.4)	0.028
Non-dihydropyridine calcium channel blockers = 1 (%)	187 (16.0)	193 (16.9)	0.022
Other antacids = 1 (%)	357 (30.6)	394 (34.4)	0.081
Peptic ulcer disease = 1 (%)	61 (5.2)	48 (4.2)	0.049
Peripheral vascular disease = 1 (%)	33 (2.8)	35 (3.1)	0.013
Proton-pump inhibitor = 1 (%)	169 (14.5)	210 (18.3)	0.104
Renal disease = 1 (%)	28 (2.4)	76 (6.6)	0.205
Statins = 1 (%)	296 (25.4)	222 (19.4)	0.144
Transient ischemic attack = 1 (%)	17 (1.5)	22 (1.9)	0.036
Venous Thromboembolism = 1 (%)	11 (0.9)	11 (1.0)	0.002
anti-diabetes drugs = 1 (%)	225 (19.3)	203 (17.7)	0.040
antiarrhythmic drugs = 1 (%)	428 (36.7)	463 (40.4)	0.077
beta-blockering agents = 1 (%)	522 (44.8)	529 (46.2)	0.029

doi:10.6342/NTU201900301

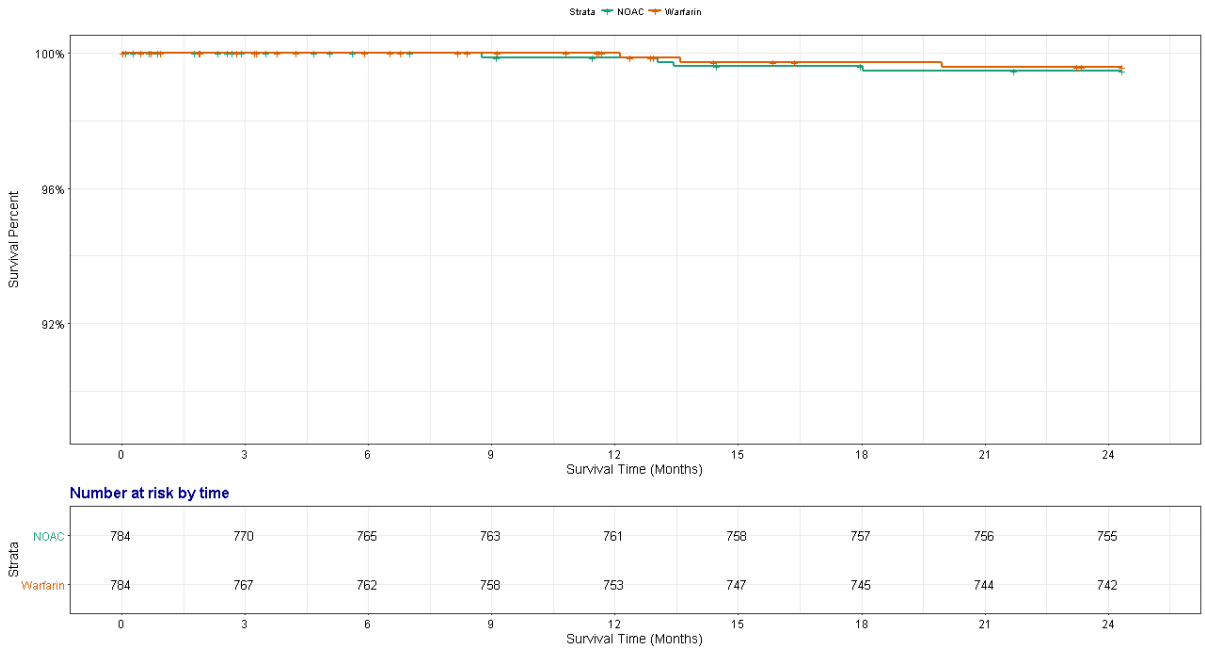
(c) Basic characteristics of the sub-cohort of intracranial hemorrhage after Propensity Score Matching.

After Propensity Score Matching

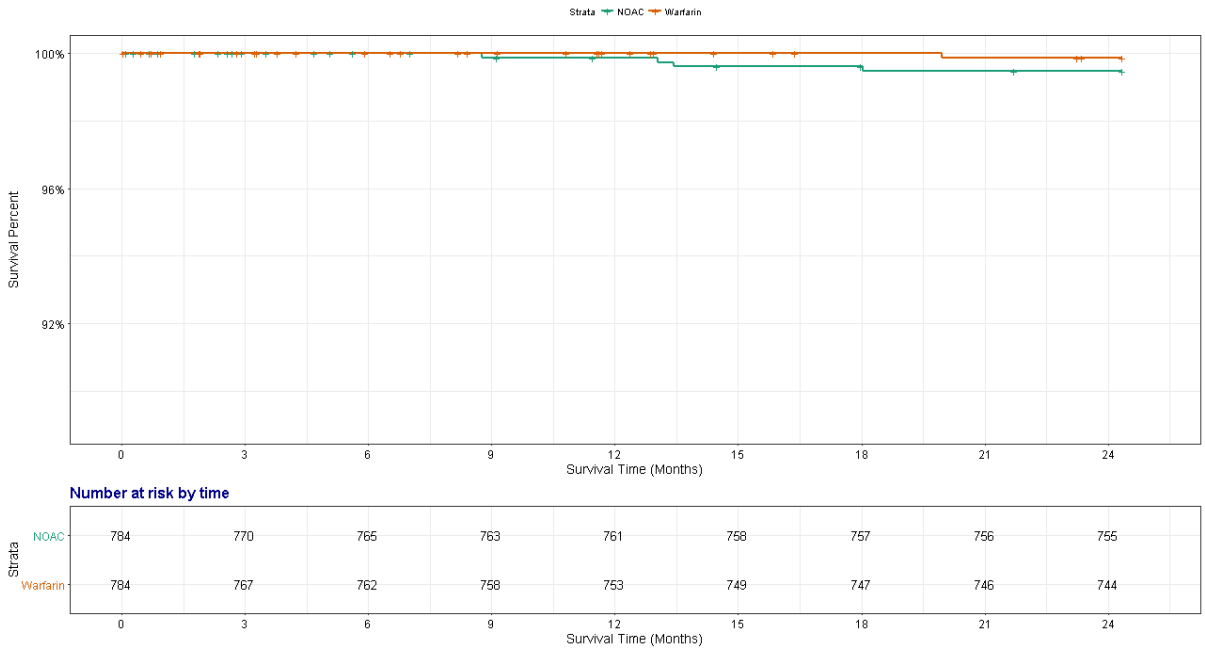
	NOAC	Warfarin	SMD
n	784	784	
ARBs/ACEIs = 1 (%)	312 (39.8)	334 (42.6)	0.057
Acute myocardial infarction = 1 (%)	11 (1.4)	13 (1.7)	0.021
Age 65-69 = 1 (%)	145 (18.5)	146 (18.6)	0.003
Age 70-74 = 1 (%)	142 (18.1)	134 (17.1)	0.027
Age 75-79 = 1 (%)	134 (17.1)	131 (16.7)	0.010
Age <65 = 1 (%)	159 (20.3)	171 (21.8)	0.038
Age >=80 = 1 (%)	204 (26.0)	202 (25.8)	0.006
Antiplatelet drugs = 1 (%)	343 (43.8)	364 (46.4)	0.054
Coagulation deficiency = 1 (%)	1 (0.1)	1 (0.1)	<0.001
Diabetes = 1 (%)	138 (17.6)	153 (19.5)	0.049
Digoxin = 1 (%)	99 (12.6)	111 (14.2)	0.045
Dihydropyridine calcium channel blockers = 1 (%)	236 (30.1)	257 (32.8)	0.058
GI bleeding = 1 (%)	24 (3.1)	14 (1.8)	0.083
Gender = 1 (%)	327 (41.7)	331 (42.2)	0.010
H2 receptor antagonist = 1 (%)	74 (9.4)	82 (10.5)	0.034
Heart failure = 1 (%)	125 (15.9)	126 (16.1)	0.003
Hypertension = 1 (%)	344 (43.9)	354 (45.2)	0.026
Ischemic stroke = 1 (%)	64 (8.2)	70 (8.9)	0.027
Liver disease = 1 (%)	30 (3.8)	21 (2.7)	0.065
NSAIDs = 1 (%)	134 (17.1)	132 (16.8)	0.007
Non-dihydropyridine calcium channel blockers = 1 (%)	133 (17.0)	132 (16.8)	0.003
Other antacids = 1 (%)	275 (35.1)	283 (36.1)	0.021
Peptic ulcer disease = 1 (%)	37 (4.7)	43 (5.5)	0.035
Peripheral vascular disease = 1 (%)	26 (3.3)	27 (3.4)	0.007
Proton-pump inhibitor = 1 (%)	135 (17.2)	145 (18.5)	0.033
Renal disease = 1 (%)	28 (3.6)	24 (3.1)	0.028
Statins = 1 (%)	150 (19.1)	170 (21.7)	0.063
Transient ischemic attack = 1 (%)	16 (2.0)	15 (1.9)	0.009
Venous Thromboembolism = 1 (%)	10 (1.3)	10 (1.3)	<0.001
anti-diabetes drugs = 1 (%)	131 (16.7)	141 (18.0)	0.034
antiarrhythmic drugs = 1 (%)	280 (35.7)	302 (38.5)	0.058
beta-blockering agents = 1 (%)	343 (43.8)	347 (44.3)	0.010

doi:10.6342/NTU201900301

(d) Kaplan–Meier Survival Plots of intracranial hemorrhage with ITT analysis



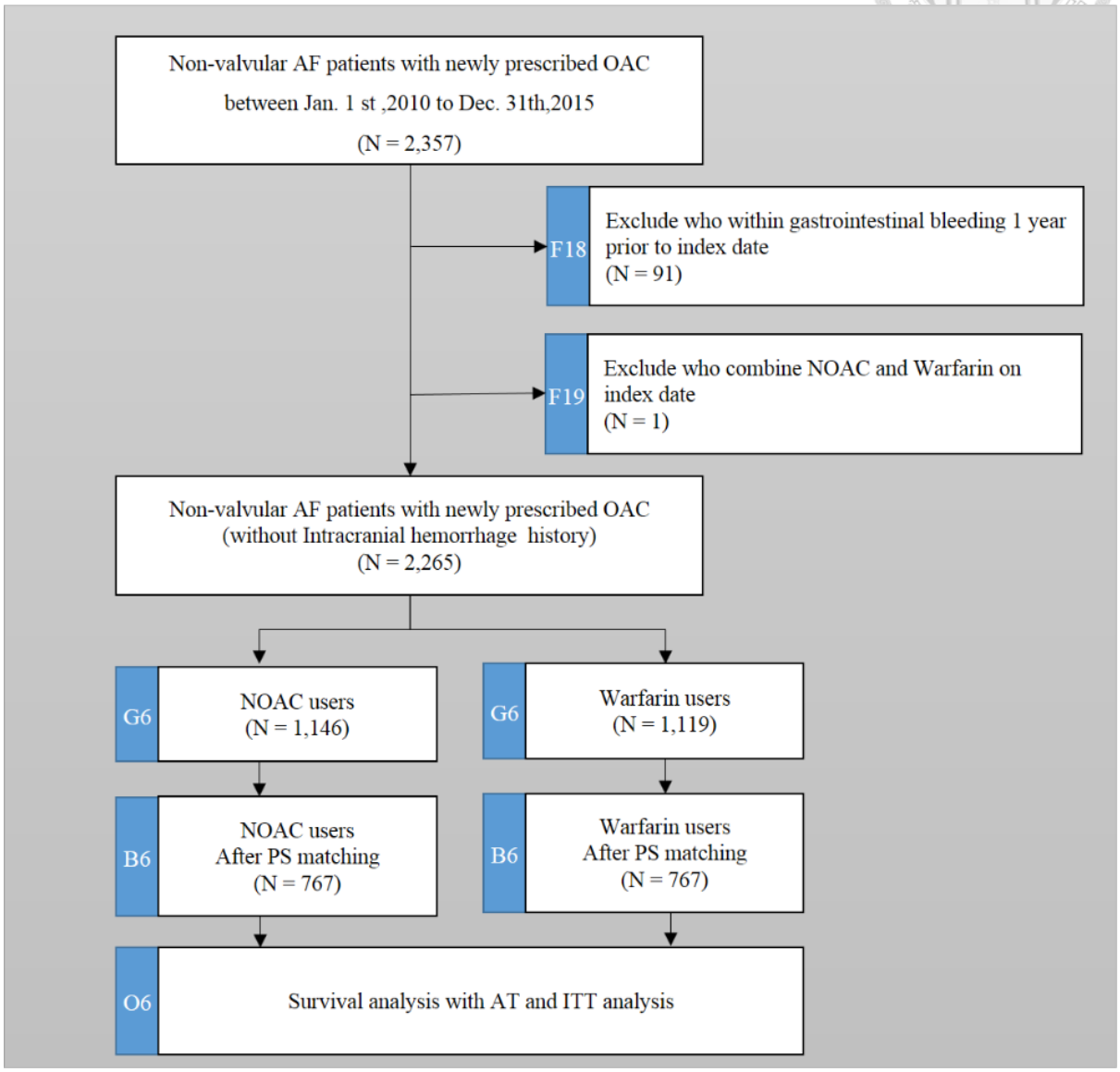
(e) Kaplan–Meier Survival Plots of intracranial hemorrhage with AT analysis



doi:10.6342/NTU201900301

5. The sub-cohort of gastrointestinal bleeding.

(a) The study flow of sub-cohort of gastrointestinal bleeding.



doi:10.6342/NTU201900301

(b) Basic characteristics of the sub-cohort of gastrointestinal bleeding before Propensity Score Matching.

Before Propensity Score Matching

	NOAC	Warfarin	SMD
n	1146	1119	
ARBs/ACEIs = 1 (%)	541 (47.2)	444 (39.7)	0.152
Acute myocardial infarction = 1 (%)	26 (2.3)	12 (1.1)	0.093
Age 65-69 = 1 (%)	186 (16.2)	160 (14.3)	0.054
Age 70-74 = 1 (%)	219 (19.1)	142 (12.7)	0.176
Age 75-79 = 1 (%)	227 (19.8)	142 (12.7)	0.194
Age <65 = 1 (%)	159 (13.9)	462 (41.3)	0.644
Age >=80 = 1 (%)	355 (31.0)	213 (19.0)	0.278
Antiplatelet drugs = 1 (%)	622 (54.3)	475 (42.4)	0.238
Coagulation deficiency = 1 (%)	1 (0.1)	3 (0.3)	0.043
Diabetes = 1 (%)	253 (22.1)	203 (18.1)	0.098
Digoxin = 1 (%)	131 (11.4)	162 (14.5)	0.091
Dihydropyridine calcium channel blockers = 1 (%)	419 (36.6)	325 (29.0)	0.161
Gender = 1 (%)	487 (42.5)	434 (38.8)	0.076
H2 receptor antagonist = 1 (%)	127 (11.1)	108 (9.7)	0.047
Heart failure = 1 (%)	181 (15.8)	174 (15.5)	0.007
Hypertension = 1 (%)	563 (49.1)	466 (41.6)	0.151
Intracranial hemorrhage = 1 (%)	11 (1.0)	6 (0.5)	0.049
Ischemic stroke = 1 (%)	96 (8.4)	96 (8.6)	0.007
Liver disease = 1 (%)	34 (3.0)	43 (3.8)	0.048
NSAIDs = 1 (%)	185 (16.1)	172 (15.4)	0.021
Non-dihydropyridine calcium channel blockers = 1 (%)	190 (16.6)	189 (16.9)	0.008
Other antacids = 1 (%)	343 (29.9)	377 (33.7)	0.081
Peptic ulcer disease = 1 (%)	52 (4.5)	37 (3.3)	0.063
Peripheral vascular disease = 1 (%)	34 (3.0)	31 (2.8)	0.012
Proton-pump inhibitor = 1 (%)	150 (13.1)	189 (16.9)	0.107
Renal disease = 1 (%)	26 (2.3)	68 (6.1)	0.191
Statins = 1 (%)	296 (25.8)	215 (19.2)	0.159
Transient ischemic attack = 1 (%)	16 (1.4)	21 (1.9)	0.038
Venous Thromboembolism = 1 (%)	10 (0.9)	11 (1.0)	0.012
anti-diabetes drugs = 1 (%)	217 (18.9)	195 (17.4)	0.039
antiarrhythmic drugs = 1 (%)	420 (36.6)	454 (40.6)	0.081
beta-blockering agents = 1 (%)	519 (45.3)	515 (46.0)	0.015

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(c) Basic characteristics of the sub-cohort of gastrointestinal bleeding after Propensity Score Matching.

After Propensity Score Matching

	NOAC	Warfarin	SMD
n	767	767	
ARBs/ACEIs = 1 (%)	297 (38.7)	320 (41.7)	0.061
Acute myocardial infarction = 1 (%)	12 (1.6)	9 (1.2)	0.034
Age 65-69 = 1 (%)	152 (19.8)	144 (18.8)	0.026
Age 70-74 = 1 (%)	134 (17.5)	129 (16.8)	0.017
Age 75-79 = 1 (%)	130 (16.9)	134 (17.5)	0.014
Age <65 = 1 (%)	158 (20.6)	161 (21.0)	0.010
Age >=80 = 1 (%)	193 (25.2)	199 (25.9)	0.018
Antiplatelet drugs = 1 (%)	339 (44.2)	344 (44.9)	0.013
Coagulation deficiency = 1 (%)	1 (0.1)	0 (0.0)	0.051
Diabetes = 1 (%)	148 (19.3)	154 (20.1)	0.020
Digoxin = 1 (%)	101 (13.2)	114 (14.9)	0.049
Dihydropyridine calcium channel blockers = 1 (%)	233 (30.4)	247 (32.2)	0.039
Gender = 1 (%)	320 (41.7)	322 (42.0)	0.005
H2 receptor antagonist = 1 (%)	77 (10.0)	83 (10.8)	0.026
Heart failure = 1 (%)	125 (16.3)	127 (16.6)	0.007
Hypertension = 1 (%)	337 (43.9)	349 (45.5)	0.031
Intracranial hemorrhage = 1 (%)	5 (0.7)	5 (0.7)	<0.001
Ischemic stroke = 1 (%)	68 (8.9)	75 (9.8)	0.031
Liver disease = 1 (%)	25 (3.3)	24 (3.1)	0.007
NSAIDs = 1 (%)	127 (16.6)	128 (16.7)	0.004
Non-dihydropyridine calcium channel blockers = 1 (%)	127 (16.6)	138 (18.0)	0.038
Other antacids = 1 (%)	263 (34.3)	274 (35.7)	0.030
Peptic ulcer disease = 1 (%)	31 (4.0)	27 (3.5)	0.027
Peripheral vascular disease = 1 (%)	22 (2.9)	22 (2.9)	<0.001
Proton-pump inhibitor = 1 (%)	122 (15.9)	131 (17.1)	0.032
Renal disease = 1 (%)	26 (3.4)	25 (3.3)	0.007
Statins = 1 (%)	142 (18.5)	155 (20.2)	0.043
Transient ischemic attack = 1 (%)	15 (2.0)	14 (1.8)	0.010
Venous Thromboembolism = 1 (%)	8 (1.0)	7 (0.9)	0.013
anti-diabetes drugs = 1 (%)	130 (16.9)	135 (17.6)	0.017
antiarrhythmic drugs = 1 (%)	270 (35.2)	279 (36.4)	0.024
beta-blockering agents = 1 (%)	329 (42.9)	335 (43.7)	0.016

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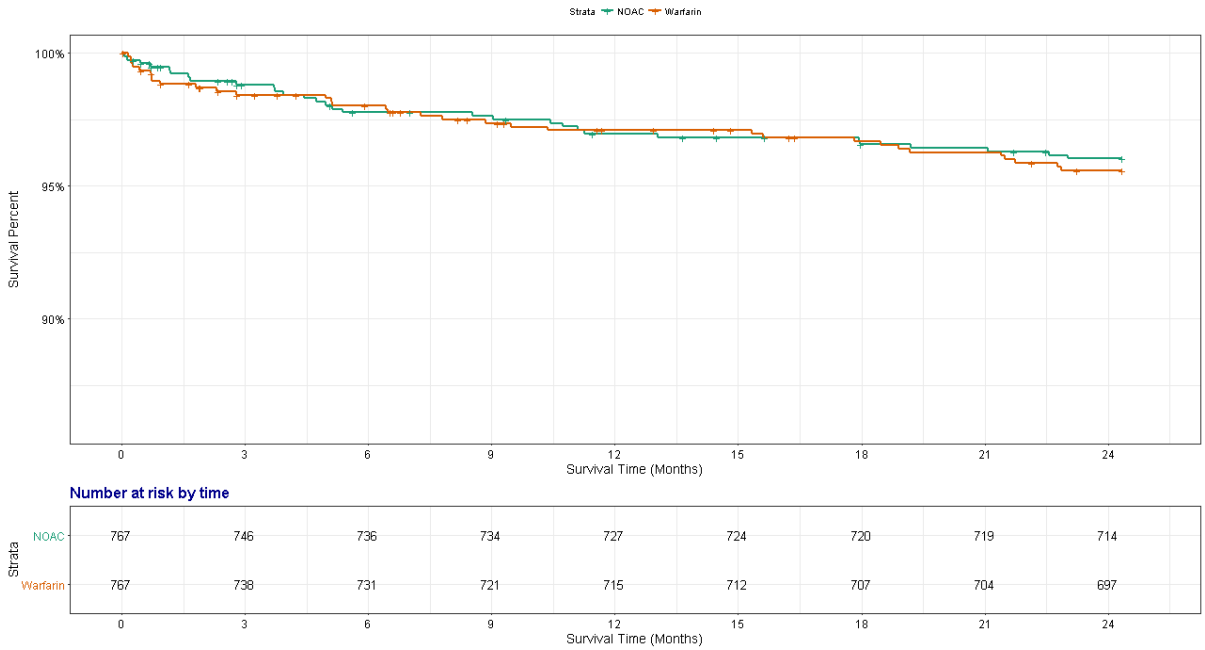
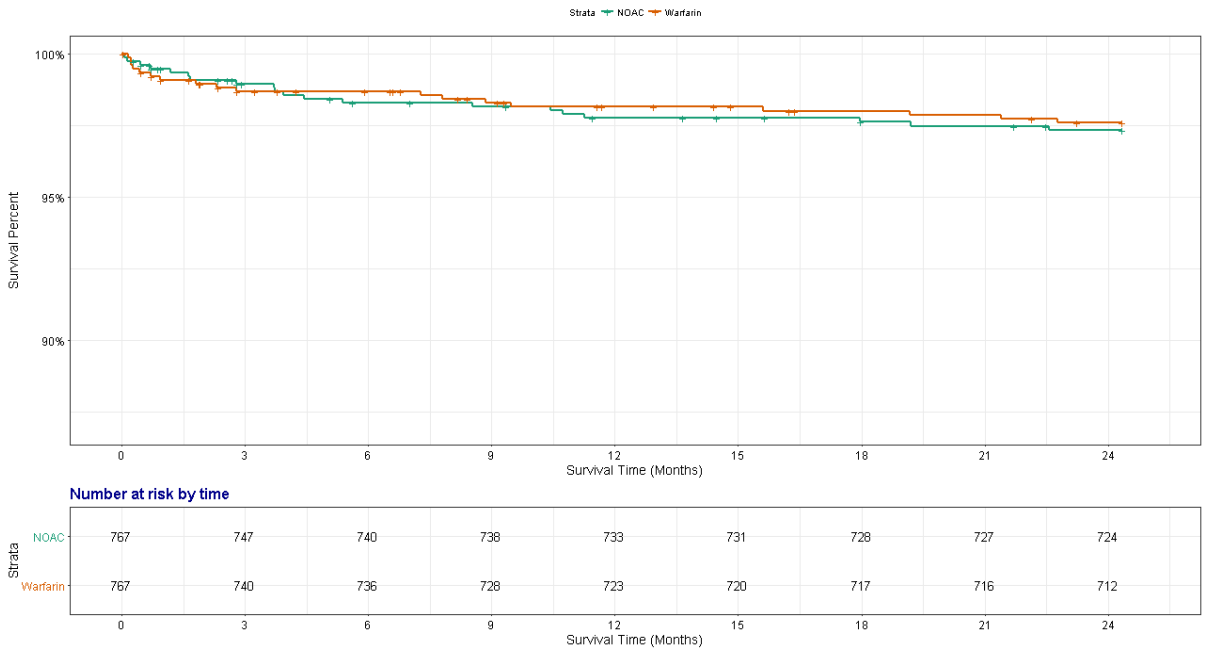
(d) Kaplan–Meier Survival Plots of gastrointestinal bleeding with ITT analysis.



(e) Kaplan–Meier Survival Plots of gastrointestinal bleeding with AT analysis.



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