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Incidence, Etiology, and Clinical Outcomes of Acute Coma

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WHAT IS ALREADY KNOWN ON THIS TOPIC

- **Acute coma with diverse causes and significant impacts on clinical course, mortality, and disability.**
- **Timely diagnosis and appropriate treatment are essential because acute coma often reflects life-threatening, systemic or intracranial processes.**
- **Heterogeneity results of acute coma studies may be due to research design and the underlying mechanism or cause are classified.**
- **Adopting secondary data for studying acute coma can provide valuable insight into preventing and treating acute coma.**

WHAT THIS STUDY ADDS

- **Using the AHRQ Clinical Classification Software (CCS) method, we propose a new clinical research model for studying acute coma, addressing the research gap**
- The incidence of acute coma is approximately 0.93 per 1,000 person-years, with older adults experiencing it at rates approximately 54 and 12 times higher than pediatric and adult groups, respectively.
- In the clinical course of acute coma, 45.49% of cases are reversible, 41.66% necessitate hospitalization, and within the 30-day mortality group, older adults constitute two-thirds.
- Infections and CNS-related diseases were the most common causes.
- The one-year follow-up after acute coma index date showed 26.54% of cases needed ICU treatment, 6.57% were complicated with a disability, and 1.88% were confined in nursing homes.

Author Statement

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2) Author contributions

CY Lin took a lead role in conceptualizing the study and writing the original draft, and was responsible for formal data analysis. CY Lin also verified the underlying data in the manuscript. MC Tsai contributed to study design, data curation, and formal data analysis, and was in charge of data collection. JF Liang and YT Huang ensured accurate data analysis and interpretation, and verified the manuscript's underlying data. YC Lee supervised the study, validated the results, and significantly contributed to reviewing and editing the manuscript. All authors participated in developing the study concept and design, analysing and interpreting data, and preparing the manuscript. We have all approved the final manuscript and agree to be accountable for all aspects of the work, promising to appropriately investigate and resolve any question related to the work's accuracy or integrity.

3) Source of support

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Declarations

1) Confirm that manuscript complies with all instructions to authors

The authors confirm that our manuscript adheres to all the instructions provided for authors.

2) Confirm that authorship requirements (see below) have been met and the final manuscript was approved by all authors

All authors, coinvestigators, and contributors know and agree to the Authorship Policies outlined in the Author Center.

3) Confirm that this manuscript has not been published elsewhere and is not under consideration by another journal

The authors confirm that this work is original, unpublished elsewhere and respectfully request its consideration for acceptance in the esteemed journal.

4) Confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate (see below). Retrospective studies require a statement regarding IRB approval

All authors have completed the ICMJE conflict of interest form and declare no conflicts of interest in relation to this manuscript. The study involved a retrospective analysis of encrypted unique personal identification data without direct patient involvement. Therefore, no patient consent was necessary for the completion of this study. As the corresponding author, I confirm

that we complied with all applicable laws regarding data protection and privacy. No patients were involved. This study was a retrospective claim data analysis that included all encrypted unique personal identification. Ethics approval: IRB of Taipei City Hospital, number-TCHIRB-10807003-E.

5) Disclose Conflicts of Interest for all authors

The authors report no disclosures relevant to the manuscript.

6) Confirm the use of reporting checklist (see below), if appropriate

The authors have confirmed the use of reporting checklists. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement when reporting observational studies and the Standards of Reporting of Neurological Disorders (STROND) for reporting incidence studies in neuroepidemiology.

7) Source of funding for the study

The research grant supported by Taipei City Hospital

ORIGINAL WORK

Incidence, Etiology, and Clinical Outcomes of Acute Coma

ABSTRACT

Objectives To investigate the clinical nature of acute coma, which will serve as a reference for subsequent clinical decision-making

Methods and analysis This observational study utilized Taiwan National Health Insurance Database to identify cases of acute coma from 2000 to 2017 based on ED discharge diagnoses. Clinical Classification Software (CCS) was employed to categorize the causes of acute coma. We examined the characteristics of acute coma cases, age-specific incidence rates, underlying causes, and clinical outcomes such as reversible coma, hospitalization, and 30-day mortality. Additionally, we assessed functional outcomes at a one-year follow-up. Long-term factors influencing mortality were ascertained using Cox regression.

Results Among 99,217,322 ED visits between 2000 and 2017, 419,480 acute coma events were identified, with an event rate of 4.23 per 1,000 ED visits and an incidence rate of 0.93 per 1,000 person-years. We analyzed 205,747 first-ever acute coma cases, predominantly male (58.90%), aged 58.27 years (SD 23.04). Infection and CNS causes were predominant. CNS and drug-related causes contributed to increased 30-day mortality, while psychiatric, alcohol, women's health and perinatal care, and seizure are causes linked to reversible coma. Patients needed intensive care (26.54%), life-sustaining treatments (41.09%), or disability (6.57%). Generalized estimating

equations revealed that CNS (aOR, 0.68; 95% CI, 0.62 to 0.74; p < .0001) and drug-related causes (aOR, 0.72; 95% CI, 0.65 to 0.81; p < .0001) were less likely to result in reversible coma, suggesting higher 30-day mortality risk factors. Cox regression showed drugs (aHR, 1.30, 95% CI 1.20 to 1.41, p < .001), neoplasm (aHR, 1.18, 95% CI 1.11 to 1.25, p < .001), and symptoms (aHR, 1.44, 95% CI 1.24 to 1.67, p < .001) elevated the long-term death risk.

Conclusion Our study demonstrates the use of ICD codes aggregation to CCS in acute coma clinical study, providing insights into its clinical nature.

Keywords

Coma, Clinical Classifications Software, Incidence, Risk factors, Natural history studies, Prognosis

Search Terms

Clinical Neurology: Coma,

Epidemiology: Incidence studies,

Epidemiology: Risk factors in epidemiology,

Epidemiology: Natural history studies (prognosis),

Clinical Neurology: Prognosis

INTRODUCTION

Acute coma is a critical time-sensitive condition with heterogeneous causes that requires urgent attention and has significant impacts on patients and healthcare professionals [1]. It is characterized by profound failure of the neurological system responsible for maintaining arousal and awareness, leading to either a reflex response or no response to external stimuli at all [2]. Prior studies estimate that 1-5% of patients presenting to the emergency department (ED) have a disturbance in consciousness [3 4]. Emergency care researchers often categorize acute coma into three etiological factors: primary CNS disease, severe medical conditions that affect the CNS secondarily, or functional such as psychogenic disorder [5 6]. The clinical course of acute coma has been classified into three main categories: reversible coma, where patients recover quickly after ED management and can be discharged without any functional deficits; mortality group consisting of patients who do not survive their coma event despite medical interventions; and hospitalization group, which includes patients requiring hospitalization that may need intensive care or life-sustaining treatments (LSTs), or complicated with long-term disabilities [7 8]. Major challenge in studying acute coma is its heterogeneous nature, with multiple contributing factors often present in a single patient. Variations in acute coma study results may arise due to differences in definitions, cause classifications, and follow-up periods [9]. These factors can affect outcomes and complicate direct comparisons between studies, underscoring the need for standardized methodologies [10]. Despite the urgent need for a better understanding clinical nature of acute coma, there is a lack of large-scale longitudinal studies

that can comprehensively address the incidence, causes, clinical course, and outcomes of acute coma.

The Agency for Healthcare Research and Quality (AHRQ) has developed the Clinical Classification Software (CCS) to provide a standardized method for classifying diagnosis codes into CCS categories based on clinical characteristics [11 12]. The CCS categories employ the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Clinical Modification (ICD-10-CM) classification systems to aggregate large numbers of ICD diagnostic codes into 285 clinically meaningful categories, thereby making clinical research more feasible. Our study aims to (1) estimate acute coma incidence, (2) use the CCS to identify acute coma causes, and (3) investigate the clinical course and outcomes.

MATERIALS AND METHODS

Study design and setting

In this observational study, we utilized Taiwan National Health Insurance Research Database (NHIRD) to examine ED visits between January 1, 2000, and December 31, 2017. The NHIRD, managed by the Ministry of Health and Welfare, offered a comprehensive dataset with information on demographics, comorbidities, hospitalization, functional status, and mortality. This study was conducted with the approval of the local ethics board and involved no direct patient interaction. We carried out a retrospective analysis of claims data, ensuring all personal identifiers were encrypted to uphold patient confidentiality.

Acute coma participants definition

Given the nature of this study, we utilized the NHIRD dataset to investigate acute coma incidences.

However, it should be noted that the NHIRD dataset lacks specific indicators like the Glasgow Coma Scale (GCS) to represent coma status. Consequently, we relied on the judgment of emergency physicians in diagnosing acute coma instances, especially in cases where there was no explicit diagnosis but an indication of coma in the ED's diagnoses. We employed International Classification of Diseases (ICD) codes to define acute coma objectively. These codes encompass a range of acute coma conditions, including "780.01" for comatose, "780.09" for other alterations of consciousness, "R40.0" for somnolence, "R40.1" for stupor, "R40.2" for unspecified coma, and "S06.7" for intracranial injury-related coma. Therefore, our study population consisted of cases that included any of these codes within the three diagnoses upon ED discharge records and remained as the final research cohort (Figure 1). The present study implemented several exclusion criteria to ensure precise estimation of the cause, disease progression, and clinical outcomes associated with acute coma. First, we omitted cases lacking comprehensive sociodemographic data. Second, we excluded those who were undergoing life-sustaining treatments or were disabled or residing in a nursing home prior to the acute coma event. Additionally, cases diagnosed with acute coma in the ED that CCS could not further classify were removed from the study. To rule out hospitalizations potentially unrelated to the acute coma events, we excluded samples hospitalized more than 14 days following the acute coma.

Incidence estimates

We estimated the annual acute coma event rate from 2000 to 2017, with acute coma events as the unit of analysis. The event rate of acute coma is calculated by dividing the number of events by ED

visits. In addition, we determined crude age group-stratified incidence rates were determined per 1000 person-years, with denominators based on the number of insured individuals during the year, taking into account their survival status and the person-years they contributed within that year. Considering insured individuals' survival status and person-years contributed and reported age-specific incidence rates in pediatric (1-18), adult (19-64), and senior adult (65+) groups with corresponding summary statistics.

Clinical course, causes and outcomes assessment

The study explored the **clinical course** of acute coma using each patient's first-ever event as the unit of analysis. Index date was set as the date of first diagnosis acute coma. ED visits were categorized into reversible coma, hospitalization, and 30-day mortality [13]. Individuals who died within 30 days of the acute coma ED index date were classified as the 30-day mortality group. Those requiring hospitalization within seven days post-episode but not dying within 30 days constituted the hospitalization group. Patients diagnosed with acute coma in the ED without needing hospitalization or facing death were categorized as the reversible coma group.

Using CCS methodology [12 14 15], we categorized ICD codes from death or hospitalization into 23 **acute coma causes** (Supplementary Table 1) and a statistical analysis plan is available in the (Supplementary Program). The diagnosis sequence began with death, hospitalization, and ED diagnosis if no death or hospitalization occured. These causes were further classified into three **etiological mechanisms**: (1) primary CNS diseases (neurological etiology), (2) medical conditions affecting the CNS secondarily (medical etiology), and (3) functional etiology[5]. Neurological

etiology included acute CNS insult, chronic neurodegenerative encephalopathy, paroxysmal seizure disorders, and brain trauma. Medical etiology included alcohol-related coma, drugs, and organ system dysfunction. Functional factors included psychogenic disorders, symptoms, syncope, and other related causes. Patients were followed for one year to evaluate short-term outcome (30-day mortality or reversible course) and long-term outcomes (ICU admission, LSTs [16], rehabilitation, disability status, or nursing home residency).

Statistical analysis

We used χ^2 tests to analyze baseline categorical characteristics and compared continuous variables' mean among coma groups with One-Way ANOVA. Generalized estimating equations (GEE) were used to estimate the adjusted odds ratio (aOR) of acute coma, accounting for multiple causes and covariates like sex, age, CCI, occupation, urbanization, and income. Survival analysis was conducted for reversible and hospitalization groups, tracking survival probability and calculating time to event (death) or censoring. Cox regression investigated potential death event causes, with hazard ratios identifying factors affecting long-term outcomes. Analyses were performed with SAS software, version 9.4, and a significance level of $p < 0.05$.

RESULTS

Cohort characteristics and clinical course estimate

Among 99,217,322 ED visits between 2000 and 2017, 419,480 acute coma events were identified. Of these, 365,675 patients were discharged or hospitalized within seven days. After excluding 4,385 ED visits with only acute coma diagnosis code, lacking further information, and participants lacking

sociodemographic data or with prior nursing home or disabled status, 205,747 cases remained in the final research cohort (Fig. 1). The cohort clinical course classified 93,598 (45.49%) as reversible acute coma group, 85,712 (41.66%) as hospitalization group, and 26,437 (12.85%) as 30-day mortality group. The study population was 54.39% male, with an average age of 58.27 (SD 23.04) years (Table 1).

Incidence of acute coma

Table 2 analyzes ICD diagnosis codes for acute coma events, revealing: (1) a crude event rate of 4.23 per 1,000 ED visits, (2) an average incidence rate of 0.93 per 1,000 person-years, and (3) age-specific incidence rates: 0.13 for pediatric, 0.57 for middle-aged, and 7.13 for senior adult groups. A significant mean decrease in incidence rate in 2016 suggests that age and temporal factors may influence acute coma incidence.

Causes and outcomes of acute coma

Table 1 presents leading acute coma causes, including infection (15.10%), CNS (14.61%), digestive (9.67%), cardiovascular (9.41%), and trauma-related (8.65%). Common reversible causes included infection (15.72%), trauma (10.89%), digestive (10.00%), women's health and perinatal care (9.56%), and CNS (8.74%). Hospitalization for acute coma frequently resulted from CNS (17.08%), infection (16.34%), cardiovascular (9.51%), digestive (9.30%), and diabetes and insulin (6.45%). Leading causes of death were CNS (27.40%), cardiovascular (12.41%), digestive (9.73%), trauma (9.10%), and infection (8.87%). Medical etiologies were the primary factor (66.75%), with neurological (27.60%) and functional (5.65%) etiologies also contributing. Short-term outcomes

indicated 45.49% of cases left the ED without sequelae, 12.85% experienced 30-day mortality, and 41.66% necessitated hospitalization within seven days. Elderly patients had a significantly higher mortality rate of 62.56% compared to 11.56% for younger patients. The one-year follow-up showed ICU treatment (26.54%), LSTs (41.09%), rehabilitation (14.23%), disability (6.57%), and nursing care (1.88%).

Multivariate analysis of acute coma

The GEE analysis identified covariates significantly associated with increased acute coma mortality, including females, older age, higher Charlson Comorbidity Index (CCI) scores, low income, and rural residence (Table 3). Compared to other causes, CNS (adjusted odds ratio [aOR], 0.68; 95% CI: 0.62 to 0.74; p < .0001) and drug-related causes (aOR, 0.72; 95% CI: 0.65 to 0.81; p < .0001) had lower odds of reversible coma compared to 30-day mortality, while psychiatric (aOR, 57.02; 95% CI: 34.11 to 95.33; p < .0001), alcohol (aOR, 33.8; 95% CI: 21.81 to 52.38; p < .0001), women's health and perinatal care (aOR, 11.86; 95% CI: 10.11 to 13.92; p < .0001), seizures (aOR, 8.32; 95% CI: 6.15 to 11.24; p < .0001), and musculoskeletal/integumentary causes (aOR, 8.16; 95% CI: 7.04 to 9.47; p < .0001) had higher odds. Drug causes had lower odds of hospitalization compared to mortality (aOR, 0.82; 95% CI: 0.73 to 0.91; p=.0003), while psychiatry (aOR, 48.29; 95% CI: 28.88 to 80.77; p < .0001), seizure (aOR, 9.01; 95% CI: 6.67 to 12.17; p < .0001), women's health and perinatal care (aOR, 5.44; 95% CI: 4.63 to 6.40; p < .0001), and alcohol (aOR, 5.20; 95% CI: 3.31 to 8.17; p < .0001) causes increased the odds. Compared to functional etiology, neurological etiology had lower odds of reversible coma (aOR, 0.55; 95% CI, 0.51 to 0.59, p < .0001) and

hospitalization (aOR, 0.70; 95% CI 0.65 to 0.75, p < .0001), while medical etiology had higher odds of reversible coma (aOR, 1.39; 95% CI: 1.30 to 1.49, p < .0001) and hospitalization (aOR, 1.16; 95% CI: 1.09 to 1.25, p < .0001).

The Kaplan-Meier estimation (Supplementary Fig. 1) and Cox proportional hazards regression (Table 4) revealed increased mortality risk associated with higher CCI score (adjusted hazard ratios [aHR], 1.08, 95% CI 1.07 to 1.09, p < .001), older age (aHR, 2.17, 95% CI 2.13 to 2.22, p < .001), manual labor (aHR, 1.03, 95% CI 1.02 to 1.04, p < .001), drug (aHR, 1.30, 95% CI 1.20 to 1.41, p < .001), neoplasm (aHR, 1.18, 95% CI 1.11 to 1.25, p < .001), and symptoms cause (aHR, 1.44, 95% CI 1.24 to 1.67, p < .001). In addition, the average mortality post-acute coma for the reversible group was observed at 7.10 years, while for the hospitalization group, it occurred at 6.41 years.

Sensitivity test of acute coma

To assess the robustness of our findings, we focused on the definition of an acute coma cohort, explicitly examining the first-ever episode that led to hospitalization within either a 7-day or 14-day period. Our analysis revealed no significant differences between these two cohort definitions in terms of clinical course subgroup distribution and cause classification for acute coma (see Supplementary Table 2). This suggests that our findings are consistent and reliable across different definitions.

DISCUSSION

Acute coma frequently represents a common pathway of organ dysfunction from diverse causes, significantly impacting patients' survival and quality of life and straining healthcare resources. This study aims to explore the incidence density , causes, clinical courses, and outcomes of acute coma. Several methodological and result issues warrant discussion.

Methodology discussion

In our 18-year longitudinal retrospective cohort study, we utilize the ICD coding system alongside the CCS method to navigate the complex etiology of acute coma. This complexity, stemming from an array of reversible and time-sensitive factors, creates challenges in synthesizing diverse clinical causes into a unified cohort for claims-based research. Previous studies have often relied on medical record reviews [17] or rigorously designed cohort studies[18], lacking a comprehensive and longitudinal perspective. To bridge this research gap, we have devised an innovative clinical research model that integrates big data analytics with clinical investigation. This approach offers a novel framework for examining the multifaceted clinical scenarios related to acute coma through claims-based data, thereby opening new avenues for neuroscientific research and enhancing emergency medical decision-making systems.

Study design, population and cohort definition

The Taiwan NHIRD, encompassing the entire population and offering comprehensive medical services, facilitated a thorough analysis of acute coma's clinical nature. Besides, The large cohort of over 200,000 patients offered a robust population representation. Moreover, we defined the

cohort based on one impaired consciousness in the ED study, where the average hospitalization duration was 6.4 days. Thereforee we included acute coma onset and hospitalization within seven days as our study cohort [19]. By excluding patients with prior nursing home residence or disability status, provids a better understanding of the true incidence and outcomes of first-ever acute coma. Meanwhile, the lack of clinical coma scale data raises concerns about the methodology accuracy, which relied on ICD coding and the CCS method. Our study adopted a broader definition of acute coma, using ICD codes, covering various alterations of consciousness such as somnolence, stupor, unspecified coma, and intracranial injury-related coma. Our study adopted a broad range of acute coma diagnosis codes to capture various clinical scenarios [20]. We used ICD coding methodology covering the qualitative spectrum of 'decreased consciousness,' including somnolence, stupor, coma, and quantitative GCS score ranges [20]. We also included the current quantitative approach to coma assessment, coding GCS scores of 13-15 as R40.0, 9-12 as R40.1, and ≤ 8 as R40.2. This approach ensured a thorough representation of acute coma in our research sample.

Defined of acute coma cause

Integrating CCS with the ICD coding system in clinical research potentially offers a holistic and nuanced methodology for categorizing complex clinical data into clinically meaningful classes [14]. While established frameworks for transforming a myriad of ICD codes into clinically relevant categories that can guide clinical decision-making, inform policy interventions, or enable regular monitoring are not yet widespread [12], In our study, we utilized CCS to condense 285 CCS categories

into 23 clinically relevant causes of acute coma, rendering the study practically feasible and enabling the in-depth analysis of acute coma's multifaceted clinical manifestations. This approach facilitates large-scale, longitudinal population-based studies in EDs, optimizing approaches to address acute coma's clinical nature.

Results discussion

Understanding the clinical characteristics of acute coma makes it crucial for intensivist clinicians to identify the cause to prevent disability [21] and emergency medical policy applications.

Causes, clinical courses, and outcomes

Infections, CNS disorders, digestive issues, cardiovascular events, and trauma are leading causes of acute coma. Our research results are consistent with international findings, with infection being the most common cause [22 23]. Acute coma causes differ based on geography [24] or age [22]. For instance, poisoning contributes to approximately one-third of unconsciousness cases in Nordic countries [24]. In children, common causes are intoxication, epilepsy, infection, and traumatic brain injury [17]. In adults and older adults, CNS and infectious disorders are more common [17 20]. The prominence of digestive causes for acute coma in our cohort may be due to the prevalence of hepatitis and hepatocellular carcinoma in Taiwan [25]. To facilitate a broader understanding of public health implications related to the potential etiologies and mechanisms underlying acute coma, and to enable meaningful comparisons with existing literature, we have classified the etiologies of acute coma into three major categories: neurological, medical, and functional factors[5 6 26]. This categorization approach aids in the development of targeted intervention strategies and informs policy-making.

Neurological causes account for about one-third of cases, while non-neurological causes comprise the remaining two-thirds [27]. Schmidt (2017) reported that neurological and medical etiologies each contributed to about 50% of acute coma cases [5]. Functional or psychogenic coma constituted around 5% of cases. It is worth further exploring the causes of coma resulting from functional factors.

The clinical course of acute coma varies due to differing underlying causes or etiologies [9 22]. Over half of first-ever acute coma patients required hospitalization or faced mortality, whereas the other near half demonstrated reversible outcomes. Short-term in-hospital mortality rate for patients with acute coma is about 5 -11% [3 19 28] with longer follow-up reaching 25% [28]. Our study found that 27.60% of acute coma cases were attributed to neurological etiology, and within the mortality group, 38.16% of cases had a neurological cause. This supports prior research indicating that clinical course is highly dependent on etiology [22]. Syncope and seizures are generally believed to be the most common causes of reversible coma. However, in our study, these two common causes accounted for only 1.33% of cases of overall acute coma. This may support researchers' definition of coma as a state of prolonged sustained unconsciousness lasting at least one hour [29]. Our emergency physicians may better understand syncope and seizure, improving diagnostic accuracy [30]. Study showed that twenty percent of patients with acute coma may have already been reversible on admission [28]. If these patients are monitored for two months after hospitalization, one-third of them may fully recover consciousness [31]. Our study found that approximately 45.49% of patients had

reversible coma. The higher proportion of reversible coma in our study may reflect a more lenient coding of coma or the higher quality of emergency medical care by emergency physicians in our study. These results suggest that the outcome of acute coma is highly dependent on the underlying cause and severity of the condition [32]. Regarding long-term outcomes, one-quarter of patients with first-ever acute coma necessitated ICU admission, and forty percent required LSTs within one year. The high percentage of patients in the LSTs group, who require long-term care and have a high mortality rate, emphasizes the need for improved management strategies for patients with acute coma [7].

Incidence

Our study found an acute coma event rate of 4.23 visits per 1,000 ED visits, consistent with the Schmidt et al. (2019) ED cohort study [28]. However, our results differ from another study that reported 0.29-0.40 cases of coma per 1,000 ED visits [33]. Based on the ICD code approach, studies suggested that acute coma is about 0.93-5% of all ED visits [27 34]. Pediatric non-trauma coma studies also have reported incidences ranging from 0.3 to 1.6 per 1,000 person-years [22]. This disparity in results may be attributed to differences in research questions, study design, study population, or definitions [35].

We investigated the incidence rates of acute coma in different age groups and temporal trends. The highest incidence rate of acute coma was observed in the elderly age group, emphasizing the significance of this public health concern in the aging population. However, there is also some variability in the incidence rates over time. We found that the incidence rate stabilized at around 1

per 1,000 person-years from 2007 to 2015 and observed a significant mean decrease in the incidence rate in 2016 compared to previous years. Specifically, there was a significant mean decrease from 0.73 per 1,000 person-years in 2016 to 0.63 per 1,000 person-years in 2017. One possible explanation for the decrease in acute coma incidence during 2016-2017 is the transition from the ICD-9 to ICD-10 coding system in 2015. We also found that there was no significant difference in the number of ED visits between 2014 and 2017 (5,904,262 vs 5,945,444, respectively). Thus, the significant change in acute coma incidence could be an artifact of the ICD coding transition effect [36].

Strengths and Limitations

This study has several strengths and limitations. Strengths include using nationwide longitudinal data to observe first-ever acute coma patterns, enabling tracking of clinical progression. The average post-acute coma mortality occurring seven years highlights its importance as a risk factor and common pathway for mortality. Additionally, the study employed AHRQ CCS methodology, facilitating regular monitoring of acute coma clinical information and enabling tailored intervention plans.

The present study has several limitations that need to be acknowledged. Firstly, the absence of a coma scale to accurately define the first-ever acute coma cohort represents a significant limitation. Instead, the study relied on acute coma-related diagnoses coded by emergency physicians in the ED, potentially leading to an underestimation of acute coma incidence and compromising the accuracy of identifying the causes of coma. Additionally, the conversion between ICD-9 and ICD-10 coding

systems may introduce inaccuracies in estimating coma-related diagnoses due to potential discrepancies and inconsistencies in classification. Consequently, the reliability of the results may be affected. Furthermore, it is important to recognize that the acute coma diagnosis employed in this study may not fully capture the underlying causes or medical utilization, as multiple contributing pathologies could be involved due to potential multiple underlying pathologies [28]. The complexity of coma etiology, along with the potential presence of various underlying factors, may limit the accuracy of attributing the diagnosis to a single cause. Moreover, a small proportion (about 2%) of acute coma patients presented in the ED lacked further diagnostic information, which reflects the challenge in diagnosing cases of coma with unknown origins and introduces potential uncertainty and incomplete data in the analysis. Another limitation is the reliance on data limited to the year 2017, preventing the examination of the potential effects of the COVID-19 pandemic. Incorporating the impact of the pandemic would have enhanced the understanding of the significance of infections and central nervous system-related causes in estimating acute coma incidence. Finally, it should be noted that this study did not utilize the World Health Organization's (WHO) World Standard Population for age-specific rates adjustment, which may limit the generalizability and comparability of the findings with other studies that utilize standardized rates based on the WHO standard populations. These limitations should be considered when interpreting the study's results, and future research should address these limitations to enhance the robustness and applicability of the findings.

CONCLUSION

Acute coma often represents a common pathway of organ dysfunction with diverse causes or etiologies, significantly impacting mortality and disability. Our study demonstrates the innovative use of ICD code aggregation to CCS in acute coma clinical study, providing valuable insights into its clinical nature. This research model has the potential to facilitate international comparative studies of acute coma characteristics using health databases.

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Author contributions CY Lin took a lead role in conceptualizing the study and writing the original draft, and was responsible for formal data analysis. CY Lin also verified the underlying data in the manuscript. MC Tsai contributed to study design, data curation, and formal data analysis and was responsible for data collection. JF Liang and YT Huang ensured accurate data analysis and interpretation and verified the manuscript's underlying data. CC Liu and YC Lee supervised the study, validated the results, and significantly contributed to reviewing and editing the manuscript. All authors participated in developing the study concept and design, analyzing and interpreting data, and preparing the manuscript. We have all approved the final manuscript and agree to be accountable for all aspects of the work, promising to appropriately investigate and resolve any question related to the work's accuracy or integrity.

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Declarations

1) Confirm that manuscript complies with all instructions to authors

The authors confirm that our manuscript adheres to all the instructions provided for authors.

2) Confirm that authorship requirements (see below) have been met and the final manuscript was approved by all authors

All authors, coinvestigators, and contributors know and agree to the Authorship Policies outlined in the Author Center.

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The authors confirm that this work is original, unpublished elsewhere and respectfully request its consideration for acceptance in the esteemed journal.

4) Confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate (see below). Retrospective studies require a statement regarding IRB approval

All authors have completed the ICMJE conflict of interest form and declare no conflicts of interest in relation to this manuscript. The study involved a retrospective analysis of encrypted unique personal identification data without direct patient involvement. Therefore, no patient consent was necessary for the completion of this study. As the corresponding author, I confirm that we complied with all applicable laws regarding data protection and privacy. No patients were involved. This study was a retrospective claim data analysis that included all encrypted unique personal identification. Ethics approval: IRB of Taipei City

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5) Disclose Conflicts of Interest for all authors

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6) Confirm the use of reporting checklist (see below), if appropriate

The authors have confirmed the use of reporting checklists. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement when reporting observational studies and the Standards of Reporting of Neurological Disorders (STROND) for reporting incidence studies in neuroepidemiology.

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Table 1 Characteristics of acute coma cohort

	Total acute coma n (%)		Reversible coma n (%)		Hospitalization n (%)		30-day mortality n (%)		*p*-value
Total	205,747	(100·00)	93,598	(45·49)	85,712	(41·66)	26,437	(12·85)	<0·001
Sex									
Male	111,897	(54·39)	49,738	(53·14)	46,910	(54·73)	15,249	(57·68)	<0·001
Female	93,850	(45·61)	43,860	(46·86)	38,802	(45·27)	11,188	(42·32)	
Age	58·27	±23·04	39·81	±19·99	52·93	±22·93	70·99	±16·90	<0·001
Age group									
<18	61,756	(30·02)	38,509	(13·56)	19,661	(22·94)	3,586	(13·56)	<0·001
18-64	49,039	(23·83)	22,955	(23·88)	19,771	(23·07)	6,313	(23·88)	
≧65	94,952	(46·15)	32,134	(62·56)	46,280	(53·99)	16,538	(62·56)	
CCI index									
CCI≦1	133,867	(65·06)	73,552	(78·58)	46,694	(54·48)	13,621	(51·52)	<0·001
CCI>1	71,880	(34·94)	20,046	(21·42)	39,018	(45·52)	12,816	(48·48)	
Income									
Low	58,488	(28·43)	26,255	(28·05)	25,054	(29·23)	7,179	(27·15)	<0·001
Middle	73,869	(35·90)	35,899	(38·35)	29,228	(34·10)	8,742	(33·07)	
High	73,390	(35·67)	31,444	(33·60)	31,430	(36·67)	10,516	(39·78)	
Occupation									
Dependents of the insured individuals	62,271	(30·27)	27,616	(29·50)	26,700	(31·15)	7,955	(30·09)	<0·001
Civil servants, teachers, military, veterans	2,915	(1·42)	1,429	(1·53)	1,151	(1·34)	335	(1·27)	
Nonmanual workers and professionals	20,121	(9·78)	11,891	(12·70)	6,401	(7·47)	1,829	(6·92)	
Manual workers	72,036	(35·01)	29,707	(31·74)	31,824	(37·13)	10,505	(39·73)	
Other	48,404	(23·53)	22,955	(24·53)	19,636	(22·91)	5,813	(21·99)	
Urbanization									
Urban	83,476	(40·57)	41,892	(44·76)	31,882	(37·20)	9,702	(36·70)	<0·001
Suburban	76,632	(37·25)	33,150	(35·42)	33,456	(39·03)	10,026	(37·92)	
Rural	45,639	(22·18)	18,556	(19·82)	20,374	(23·77)	6,709	(25·38)	
Causes of acute coma									<0·001
Neurological cause group	56,790	(27·60)	22,153	(23·67)	24,430	(28·50)	10,207	(38·61)	<0·001
CNS	30,065	(14·61)	8,183	(8·74)	14,639	(17·08)	7,243	(27·40)	
Encephalopathy	6,700	(3·26)	2,616	(2·79)	3,573	(4·17)	511	(1·93)	
Seizure	2,225	(1·08)	1,157	(1·24)	1,020	(1·19)	48	(0·18)	
Trauma	17,800	(8·65)	10,197	(10·89)	5,198	(6·06)	2,405	(9·10)	
Medical cause group	137,330	(66·75)	65,158	(69·61)	57,007	(66·51)	15,165	(57·36)	
Alcohol	2,533	(1·23)	2,255	(2·41)	257	(0·30)	21	(0·08)	
Cardiovascular	19,367	(9·41)	7,938	(8·48)	8,148	(9·51)	3,281	(12·41)	
Diabetes and insulin	11,155	(5·42)	4,178	(4·46)	5,529	(6·45)	1,448	(5·48)	
Digestive	19,904	(9·67)	9,364	(10·00)	7,968	(9·30)	2,572	(9·73)	
Drugs	5,036	(2·45)	2,002	(2·14)	1,941	(2·26)	1,093	(4·13)	
Electrolyte	456	(0·22)	249	(0·27)	152	(0·18)	55	(0·21)	
Endocrine	2,427	(1·18)	1,086	(1·16)	904	(1·05)	437	(1·65)	
Genitourinary	3,463	(1·68)	1,836	(1·96)	1,327	(1·55)	300	(1·13)	
Hematology	587	(0·29)	292	(0·31)	228	(0·27)	67	(0·25)	
Infection	31,063	(15·10)	14,714	(15·72)	14,005	(16·34)	2,344	(8·87)	
Musculoskeletal and integumentary	6,144	(2·99)	3,659	(3·91)	2,208	(2·58)	277	(1·05)	
Neoplasm	10,062	(4·89)	3,938	(4·21)	4,459	(5·20)	1,665	(6·30)	
Renal	3,564	(1·73)	1,149	(1·23)	1,884	(2·20)	531	(2·01)	
Respiratory	9,419	(4·58)	3,550	(3·79)	5,007	(5·84)	862	(3·26)	
Women's health and perinatal care	12,150	(5·91)	8,948	(9·56)	2,990	(3·49)	212	(0·80)	
Functional cause group	11,627	(5·65)	6,287	(6·72)	4,275	(4·99)	1,065	(4·03)	
Psychiatry	4,765	(2·32)	2,923	(3·12)	1,827	(2·13)	15	(0·06)	
Symptoms	1,379	(0·67)	881	(0·94)	342	(0·40)	156	(0·59)	
Syncope	521	(0·25)	352	(0·38)	169	(0·20)	0	(0·00)	
Others	4,962	(2·41)	2,131	(2·28)	1,937	(2·26)	894	(3·38)	
Outcome									
ICU	54,614	(26·54)	0	(0·00)	39,144	(45·67)	15,470	(58·52)	<0·001
LSTs	84,538	(41·09)	10,578	(11·30)	50,056	(58·40)	23,904	(90·42)	<0·001
Rehab	29,273	(14·23)	4,816	(5·15)	23,728	(27·68)	729	(2·76)	<0·001
Nursing home	3,861	(1·88)	492	(0·53)	3,261	(3·80)	108	(0·41)	<0·001
Disable	13,514	(6·57)	2,856	(3·05)	10,629	(12·40)	29	(0·11)	<0·001

CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department; ICU: intensive care units; LST: life-sustaining treatment;

Chi-Square Test analyzed category variables distribution among groups; continue variable by One-way ANOVA·

Table 2 Acute coma event rate and incidence by year and age group

Year	ED visits	Coma events	Coma rate (‰)	Incidence (‰) (95% CI)	Age 1-18 Incidence (‰) (95% CI)	Age 19-64 Incidence (‰) (95% CI)	Age ≧ 65 Incidence (‰) (95% CI)
2000	4,519,482	10,330	2·29	0·45 (0·44-0·46)	0·08 (0·08-0·09)	0·30 (0·30-0·31)	7·74 (7·53-7·95)
2001	4,707,002	11,480	2·44	0·49 (0·48-0·50)	0·09 (0·08-0·10)	0·32 (0·32-0·33)	7·77 (7·57-7·97)
2002	5,028,446	12,567	2·50	0·53 (0·52-0·54)	0·10 (0·09-0·11)	0·34 (0·33-0·34)	7·78 (7·59-7·97)
2003	4,776,136	13,246	2·77	0·56 (0·55-0·57)	0·10 (0·09-0·10)	0·36 (0·35-0·36)	7·21 (7·04-7·38)
2004	5,354,185	16,072	3·00	0·67 (0·66-0·68)	0·11 (0·10-0·11)	0·44 (0·43-0·45)	7·58 (7·41-7·74)
2005	5,416,581	20,535	3·79	0·85 (0·83-0·86)	0·12 (0·11-0·13)	0·56 (0·54-0·57)	8·80 (8·63-8·97)
2006	5,171,689	21,769	4·21	0·89 (0·88-0·90)	0·13 (0·12-0·13)	0·57 (0·56-0·58)	8·59 (8·43-8·75)
2007	5,282,870	23,591	4·47	0·96 (0·94-0·97)	0·13 (0·12-0·14)	0·58 (0·57-0·60)	8·74 (8·59-8·89)
2008	5,191,529	25,548	4·92	1·02 (1·01-1·04)	0·14 (0·13-0·15)	0·63 (0·62-0·64)	8·53 (8·39-8·67)
2009	5,770,750	27,062	4·69	1·08 (1·07-1·09)	0·15 (0·14-0·16)	0·65 (0·64-0·67)	8·43 (8·30-8·57)
2010	5,878,033	31,184	5·31	1·23 (1·22-1·25)	0·17 (0·16-0·18)	0·73 (0·71-0·74)	9·27 (9·13-9·41)
2011	6,060,366	33,944	5·60	1·33 (1·32-1·35)	0·19 (0·18-0·20)	0·80 (0·78-0·81)	9·24 (9·11-9·37)
2012	6,098,194	34,259	5·62	1·33 (1·32-1·34)	0·19 (0·18-0·20)	0·79 (0·78-0·80)	8·60 (8·47-8·72)
2013	5,753,114	33,531	5·83	1·29 (1·28-1·31)	0·20 (0·19-0·21)	0·76 (0·75-0·77)	7·80 (7·69-7·91)
2014	5,904,262	34,917	5·91	1·34 (1·32-1·35)	0·19 (0·18-0·21)	0·78 (0·77-0·79)	7·48 (7·38-7·59)
2015	6,055,577	33,366	5·51	1·27 (1·25-1·28)	0·21 (0·19-0·22)	0·73 (0·72-0·74)	6·57 (6·47-6·66)
2016	6,303,662	19,355	3·07	0·73 (0·72-0·74)	0·09 (0·09-0·10)	0·39 (0·38-0·40)	3·70 (3·63-3·76)
2017	5,945,444	16,724	2·81	0·63 (0·62-0·64)	0·07 (0·07-0·08)	0·33 (0·32-0·34)	2·96 (2·90-3·02)
Total	99,217,322	419,480					
Average			4·23	0·93 (0·93-0·94)	0·13 (0·13-0·13)	0·57 (0·57-0·57)	7·13 (7·10-7·16)

CI: confidence interval; ED: emergency department;

Coma rate(‰)=acute coma events/1,000ED visits

Incidence of acute coma per 1,000 person-year

Table 3 Generalized linear model analysis of acute coma patients

		Reversible coma v.s. 30-day mortality				Hospitalization v.s. 30-day mortality			
		OR (95%CI)	*p*-value	aOR (95%CI)	*p*-value	OR (95%CI)	*p*-value	aOR (95%CI)	*p*-value
Sex	Male vs Female	1·20 (1·17-1·23)	<0·0001	1·29 (1·25-1·33)	<0·0001	1·13 (1·10-1·16)	<0·0001	1·14 (1·10-1·17)	<0·0001
Age	19-64 vs ≤ 18 years old	0·34 (0·32-0·35)	<0·0001	0·44 (0·42-0·46)	<0·0001	0·57 (0·55-0·60)	<0·0001	0·59 (0·56-0·62)	<0·0001
	≥ 65 vs ≤ 18 years old	0·18 (0·17-0·19)	<0·0001	0·26 (0·25-0·27)	<0·0001	0·49 (0·46-0·53)	<0·0001	0·44 (0·42-0·46)	<0·0001
CCI	> 1 vs ≤ 1	0·29 (0·28-0·30)	<0·0001	0·44 (0·42-0·45)	<0·0001	0·89 (0·87-0·91)	<0·0001	1·04 (1·01-1·07)	0·0219
Income	Middle vs low group	1·22 (1·18-1·26)	<0·0001	1·58 (1·52-1·64)	<0·0001	1·18 (1·13-1·21)	<0·0001	1·30 (1·25-1·35)	<0·0001
	High vs low group	1·37 (1·33-1·42)	<0·0001	1·33 (1·28-1·37)	<0·0001	1·12 (1·08-1·16)	<0·0001	1·12 (1·09-1·17)	<0·0001
Occupation	Dependents of the insured individuals vs others	0·82 (0·72-0·92)	0·0012	0·83 (0·73-0·95)	0·0055	0·97 (0·87-1·11)	0·7416	0·94 (0·83-1·07)	0·3469
	Civil servants, teachers, military, veterans vs others	1·53 (1·34-1·74)	<0·0001	0·93 (0·81-1·07)	0·3002	1·09 (0·89-1·16)	0·774	0·84 (0·74-0·97)	0·0136
	Nonmanual workers and professionals vs others	0·67 (0·59-0·75)	<0·0001	0·84 (0·74-0·96)	0·0084	0·88 (0·78-1·00)	0·0503	0·89 (0·78-1·01)	0·0799
	Manual workers vs others	0·93 (0·82-1·05)	0·2501	1·04 (0·91-1·18)	0·6073	0·97 (0·87-1·12)	0·8258	1·01 (0·89-1·15)	0·8776
Urbanization	Urban	0·77 (0·74-0·79)	<0·0001	0·83 (0·80-0·86)	<0·0001	1·02 (0·98-1·05)	0·3561	1·05 (1·01-1·08)	0·0064
	Urbanization	0·64 (0·62-0·66)	<0·0001	0·77 (0·74-0·80)	<0·0001	0·92 (0·89-0·96)	<0·0001	0·98 (0·94-1·02)	0·2124
Causes of coma	**Neurological group**	0·37 (0·34-0·39)	<0·0001	0·55 (0·51-0·59)	<0·0001	0·56 (0·46-0·64)	<0·0001	0·70 (0·65-0·75)	<0·0001
	CNS	0·47 (0·44-0·52)	<0·0001	0·68 (0·62-0·74)	<0·0001	0·93 (0·86-1·02)	0·1051	1·09 (1·00-1·19)	0·0517
	Encephalopathy	2·15 (1·90-2·43)	<0·0001	4·08 (3·59-4·63)	<0·0001	3·33 (3·06-3·65)	<0·0001	4·24 (3·75-4·80)	<0·0001
	Seizure	10·11 (7·50-13·64)	<0·0001	8·32 (6·15-11·24)	<0·0001	9·55 (7·09-13·24)	<0·0001	9·01 (6·67-12·17)	<0·0001
	Trauma	1·78 (1·63-1·95)	<0·0001	1·75 (1·59-1·92)	<0·0001	1·00 (0·91-1·10)	0·9585	1·02 (0·92-1·11)	0·7595
	Medical group	0·73 (0·68-0·78)	<0·0001	1·39 (1·30-1·49)	<0·0001	0·94 (0·87-1·00)	0·0641	1·16 (1·09-1·25)	<0·0001
	Alcohol	45·05 (29·11-69·72)	<0·0001	33·8 (21·81-52·38)	<0·0001	5·85 (3·60-8·88)	<0·0001	5·20 (3·31-8·17)	<0·0001
	Cardiovascular	1·02 (0·93-1·11)	0·7406	2·04 (1·86-2·24)	<0·0001	1·15 (1·05-1·25)	0·0027	1·50 (1·37-1·65)	<0·0001
	Diabetes and insulin	1·21 (1·10-1·34)	0·0001	3·13 (2·82-3·47)	<0·0001	1·76 (1·60-1·94)	<0·0001	2·31 (2·09-2·55)	<0·0001
	Digestive	1·53 (1·40-1·67)	<0·0001	2·53 (2·31-2·78)	<0·0001	1·43 (1·31-1·57)	<0·0001	1·69 (1·54-1·85)	<0·0001
	Drugs	0·77 (0·69-0·86)	<0·0001	0·72 (0·65-0·81)	<0·0001	0·82 (0·74-0·91)	0·0003	0·82 (0·73-0·91)	0·0003
	Electrolyte	1·90 (1·40-2·57)	<0·0001	2·96 (2·17-4·04)	<0·0001	1·78 (1·33-1·75)	0·1342	1·53 (1·11-2·11)	0·0091
	Endocrine	1·04 (0·91-1·19)	0·5473	1·49 (1·29-1·72)	<0·0001	0·96 (0·83-1·10)	0·5139	1·15 (1·00-1·32)	0·0521
	Genitourinary	2·57 (2·22-2·97)	<0·0001	4·41 (3·80-5·12)	<0·0001	2·14 (1·76-2·37)	<0·0001	2·59 (2·23-3·01)	<0·0001
	Hematology	1·83 (1·39-2·41)	<0·0001	2·53 (1·90-3·36)	<0·0001	1·87 (1·48-2·09)	0·0018	1·83 (1·38-2·44)	<0·0001
	Infection	2·63 (2·41-2·88)	<0·0001	4·26 (3·88-4·67)	<0·0001	2·76 (2·52-3·02)	<0·0001	3·36 (3·07-3·69)	<0·0001
	Musculoskeletal and integumentary	5·54 (4·79-6·41)	<0·0001	8·16 (7·04-9·47)	<0·0001	3·88 (3·37-4·27)	<0·0001	4·35 (3·75-5·05)	<0·0001
	Neoplasm	0·99 (0·90-1·09)	0·8747	2·06 (1·86-2·28)	<0·0001	1·14 (1·02-1·36)	<0·0001	1·57 (1·42-1·73)	<0·0001
	Renal	0·91 (0·80-1·03)	0·142	2·30 (2·01-2·62)	<0·0001	1·44 (1·25-1·86)	<0·0001	2·21 (1·95-2·51)	<0·0001
	Respiratory	1·73 (1·55-1·93)	<0·0001	3·54 (3·16-3·96)	<0·0001	2·48 (2·21-2·98)	<0·0001	3·57 (3·20-3·98)	<0·0001
	Women's health and perinatal care	17·71 (15·13-20·72)	<0·0001	11·86 (10·11-13·92)	<0·0001	6·51 (5·65-7·64)	<0·0001	5·44 (4·63-6·40)	<0·0001
	Functional group	(ref· of coma group)							
	Psychiatry	81·68 (48·90-136·46)	<0·0001	57·02 (34·11-95·33)	<0·0001	56·17 (33·69-93·92)	<0·0001	48·29 (28·88-80·77)	<0·0001
	Symptoms	2·37 (1·97-2·86)	<0·0001	2·78 (2·30-3·38)	<0·0001	1·01 (0·82-1·24)	0·9106	1·11 (0·90-1·37)	0·3158
	Syncope	NC		NC		NC		NC	
	Others	(ref of causes of coma)							

aOR: adjusted odds ratio; CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department; ICU: intensive care units; LST: life-sustaining treatment;

Syncope: no convergence

Table 4 Multivariate Cox regression analysis of factors contributing to all-cause mortality in acute coma patients

	Cox proportional hazards	
	aHR	*p*-value
Sex (male)	0·82 (0·80 - 0·84)	< 0·001
CCI (CCI>1)	1·08 (1·07 - 1·09)	< 0·001
Age (old age)	2·17 (2·13 – 2·22)	< 0·001
Income (high)	0·98 (0·97 - 1·00)	0·05
Occupation (manual)	1·03 (1·02 - 1·04)	< 0·001
Area (urban)	1·02 (1·01 - 1·04)	0·01
Neurological group		
CNS	0·83 (0·79 - 0·88)	< 0·001
Encephalopathy	0·93 (0·87 - 0·99)	0·04
Seizure	0·32 (0·26 - 0·39)	< 0·001
Trauma	0·48 (0·45 - 0·52)	< 0·001
Medical group		
Alcohol	0·39 (0·30 – 0·51)	< 0·001
Cardiovascular	0·94 (0·89 - 0·99)	0·02
Digestive	0·91 (0·86 - 0·96)	< 0·001
Drugs	1·30 (1·20 - 1·41)	< 0·001
Electrolyte	0·99 (0·78 - 1·25)	0·93
Endocrine	0·76 (0·67 - 0·86)	< 0·001
Genitourinary	0·43 (0·38 – 0·49)	< 0·001
Hematology	0·63 (0·49 - 0·80)	< 0·001
Infection	0·66 (0·63 - 0·69)	< 0·001
Musculoskeletal and integumentary	0·31 (0·28 - 0·35)	< 0·001
Neoplasm	1·18 (1·11 - 1·25)	< 0·001
Renal	1·05 (0·97 - 1·13)	0·21
Respiratory	0·80 (0·75 - 0·85)	< 0·001
Women's health and perinatal care	0·15 (0·13 - 0·18)	< 0·001
Functional group		
Psychiatry	0·05 (0·03 - 0·05)	< 0·001
Symptoms	1·44 (1·24 – 1·67)	< 0·001
Syncope	0·00	.
Others	0·47 (0·42 - 0·53)	< 0·001

Age (old age group), CCI (CCI>1 group), Income (high-income group), Area (urban), Occupation (manual), Sex (male)

Syncope: no convergence

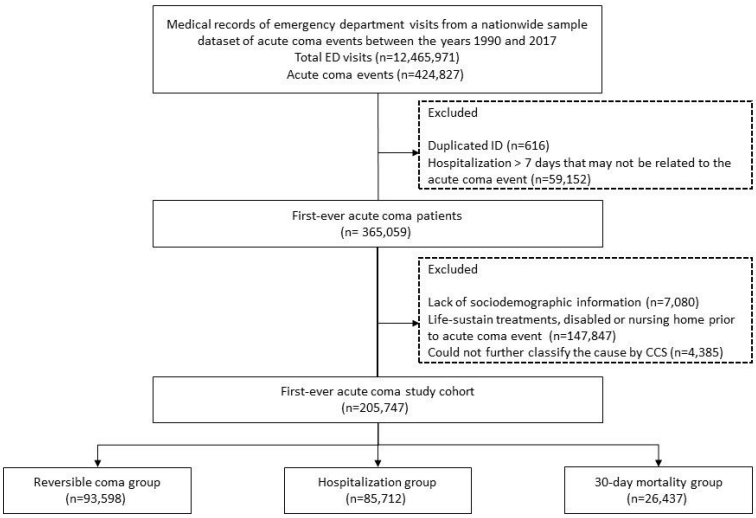

Figure 1 Flow diagram of study

STROBE Statement

—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10

Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	13

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	11-13
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13

Discussion

Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

ICMJE DISCLOSURE FORM

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Manuscript Title: Incidence, Etiology, and Clinical Outcomes of Acute Coma

Manuscript Number (if known): Click or tap here to enter text.

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		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.)	☒ None	
		We thank the Center for Public Health, Department of Education and Research, Taipei City Hospital, for providing administrative and research grant support.	
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	No time limit for this item.		
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None** The research grant supported by Taipei City Hospital	
3	Royalties or licenses	☒ **None**	
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
6	Payment for expert testimony	☒ None	
7	Support for attending meetings and/or travel	☒ None	
8	Patents planned, issued or pending	☐ None	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ None	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ None	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ None	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ None	
13	Other financial or non-financial interests	☒ None	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

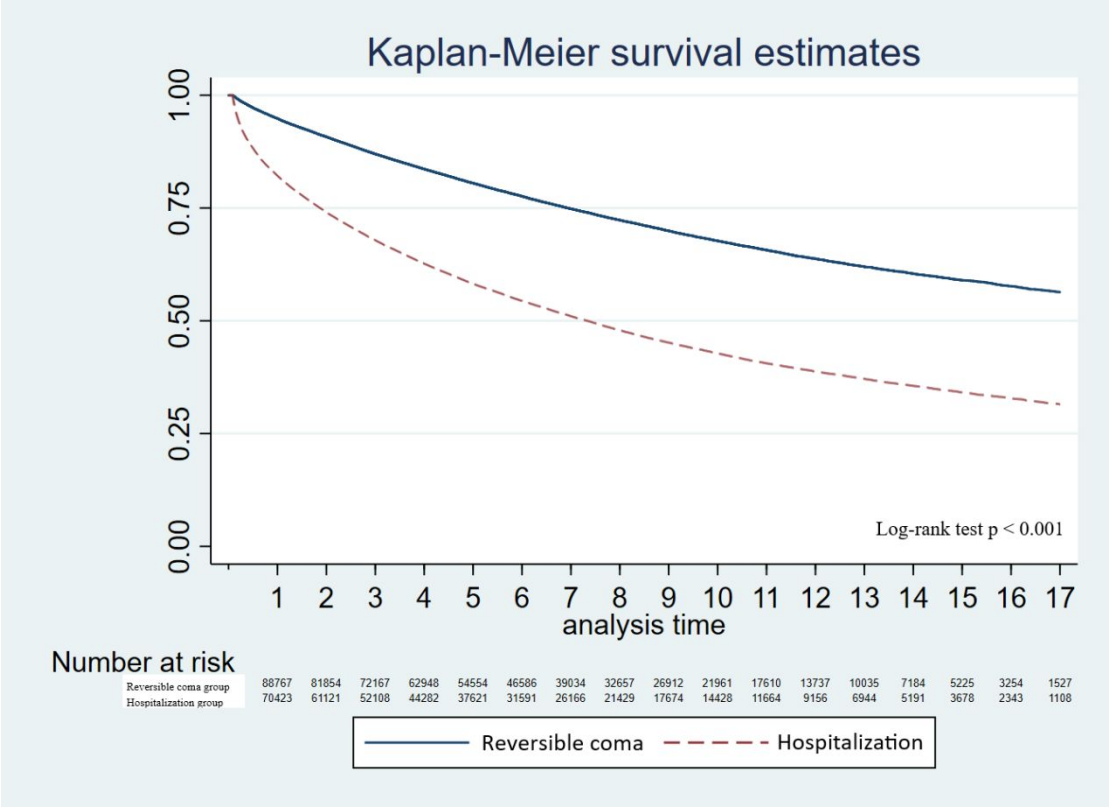

Fig. 2 Survival analysis of acute coma patients

Supplementary Table 1 Clinical classification software for grouping the causes of acute coma

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Neurological group				
Primary CNS	CNS meningitis	7,76	7,76	Meningitis (except that caused by tuberculosis or sexually transmitted disease),Viral infection
	Brain space occupied	11,35	11,35	Cancer of brain and nervous system,Cancer of head and neck
	CNS encephalitis	77,78,8	77,78,8	Encephalitis (except that caused by tuberculosis or sexually transmitted disease),Other CNS infection and poliomyelitis,Other infections; including parasitic
	Cerebrovascular disease	109,110,111,112,113,82	109,110,111,112,113,82	Acute cerebrovascular disease,Late effects of cerebrovascular disease,Occlusion or stenosis of precerebral arteries,Other and ill-defined cerebrovascular disease,Paralysis,Transient cerebral ischemia
	CNS trauma	227,228,233,234,235	227,228,233,234,235	Crushing injury or internal injury,Intracranial injury,Open wounds of head; neck; and trunk,Skull and face fractures,Spinal cord injury
Encephalopathy	Encephalopathy	79,80,81,84,95	79,80,81,84,95	Headache; including migraine,Multiple sclerosis,Other hereditary and degenerative nervous system conditions,Other nervous system disorders, Parkinson's disease
	Dementia	653	653	Delirium dementia and amnestic and other cognitive disorders,Delirium, dementia, and amnestic and other cognitive disorders
Seizure	Seizure and epilepsy	83	83	Epilepsy; convulsions

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Trauma	Trauma	225,226,229,230,231,232,236,239,240,244,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2612,2618,2619,2620,2621	0,144,145,146,147,148,149,225,226,229,230,231,232,236,239,240,244,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2612,2614,2618,2619,2620,2621	Arthroscopy,Burns,E Codes: Cut/pierceb,E Codes: Drowning/submersion,E Codes: Fall,E Codes: Fire/burn,E Codes: Firearm,E Codes: Machinery,E Codes: Motor vehicle traffic (MVT),E Codes: Other specified and classifiable,E Codes: Other specified; NEC,E Codes: Overexertion,E Codes: Pedal cyclist; not MVT,E Codes: Pedestrian; not MVT,E Codes: Place of occurrence,E Codes: Transport; not MVT,E Codes: Unspecified,External cause codes: Cut/pierce,External cause codes: Drowning/submersion,External cause codes: Fall,External cause codes: Fire/burn,External cause codes: Firearm,External cause codes: Machinery,External cause codes: Motor vehicle traffic (MVT),External cause codes: Other specified and classifiable,External cause codes: Other specified; NEC,External cause codes: Overexertion,External cause codes: Pedal cyclist; not MVT,External cause codes: Pedestrian; not MVT,External cause codes: Place of occurrence,External cause codes: Struck by; against,External cause codes: Transport; not MVT,External cause codes: Unspecified,Fracture of lower limb,Fracture of neck of femur (hip),Fracture of upper limb,Fracture treatment including reposition with or without fixation of other fracture or or dislocation,Fracture treatment including reposition with or without fixation; facial

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				fracture or dislocation,Fracture treatment including reposition with or without fixation; hip or femur fracture or dislocati,Fracture treatment including reposition with or without fixation; lower extremity fracture or disloc,Fracture treatment including reposition with or without fixation; radius or ulna fracture or disloca,Joint disorders and dislocations; trauma-related,Open wounds of extremities,Other fractures,Other injuries and conditions due to external causes,Sprains and strains,Superficial injury; contusion
	Injury and suicide	2615,662	2615,662	E Codes: Suffocation,External cause codes: Suffocation,Suicide and intentional self-inflicted injury
Medical group				
Alcohol	Alcohol	660	660	Alcohol-related disorders
Cardiovascular	Cardiovascular	100,101,102,104,105,106,107,108,114,115,116,117,118,119,121,247,96,97,98,99	100,101,102,104,105,106,107,108,114,115,116,117,118,119,121,183,96,97,98,99	Acute myocardial infarction,Aortic and peripheral arterial embolism or thrombosis,Aortic; peripheral; and visceral artery aneurysms,Cardiac arrest and ventricular fibrillation,Cardiac dysrhythmias,Conduction disorders,Congestive heart failure; nonhypertensive,Coronary atherosclerosis and other heart disease,Essential hypertension,Heart valve disorders,Hypertension complicating pregnancy; childbirth and the puerperium,Hypertension with complications and secondary hypertension,Lymphadenitis,Nonspecific chest pain,Other and ill-defined heart disease,Other circulatory disease,Other

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				diseases of veins and lymphatics,Peri-; endo-; and myocarditis; cardiomyopathy (except that caused by tuberculosis or sexually transm,Peripheral and visceral atherosclerosis,Phlebitis; thrombophlebitis and thromboembolism,Varicose veins of lower extremity
	Shock	249	249	Shock
Diabetes and insulin	Diabetes and insulin	186,49,50	186,49,50	Diabetes mellitus with complications,Diabetes mellitus without complication,Diabetes or abnormal glucose tolerance complicating pregnancy; childbirth; or the puerperium
Digestive	Digestive	120,136,137,138,139,140,141,143,145,146,147,152,153,154,155,250,251	120,136,137,138,139,140,141,143,145,146,147,152,153,154,155,250,251	Abdominal hernia,Abdominal pain,Anal and rectal conditions,Diseases of mouth; excluding dental,Disorders of teeth and jaw,Diverticulosis and diverticulitis,Esophageal disorders,Gastritis and duodenitis,Gastroduodenal ulcer (except hemorrhage),Gastrointestinal hemorrhage,Hemorrhoids,Intestinal obstruction without hernia,Nausea and vomiting,Noninfectious gastroenteritis,Other disorders of stomach and duodenum,Other gastrointestinal disorders,Pancreatic disorders (not diabetes)
	Liver	149,151,222,6	149,151,222,6	Biliary tract disease,Hemolytic jaundice and perinatal jaundice,Hepatitis,Other liver diseases
Drugs	Intoxication	241,242,243,2613,661	241,242,243,2613,661,663	E Codes: Poisoning,External cause codes: Poisoning,Poisoning by nonmedicinal substances,Poisoning by other medications and drugs,Poisoning by

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				psychotropic agents,Screening and history of mental health and substance abuse codes,Substance-related disorders
	Medication	2617	2617	Adverse effects of medical drugs,E Codes: Adverse effects of medical drugs
Electrolyte	Electrolyte	55	55	Fluid and electrolyte disorders
Endocrine	Endocrine	48,51,52,53,58	48,51,52,53,58	Disorders of lipid metabolism,Nutritional deficiencies,Other endocrine disorders,Other nutritional; endocrine; and metabolic disorders,Thyroid disorders
Genitourinary	Urogenital	160,161,162,163, 164,165,166	160,162,163,164,16 5,166,168	Calculus of urinary tract,Genitourinary symptoms and ill-defined conditions,Hyperplasia of prostate,Inflammatory conditions of male genital organs,Inflammatory diseases of female pelvic organs,Other diseases of bladder and urethra,Other diseases of kidney and ureters,Other male genital disorders
Hematology	Hematology	59,60,61,62,63,64	59,60,61,62,63,64	Acute posthemorrhagic anemia,Coagulation and hemorrhagic disorders,Deficiency and other anemia,Diseases of white blood cells,Other hematologic conditions,Sickle cell anemia
Infection	Infection	1,10,122,124,125, 126,135,142,148, 159,2,201,248,3,4 ,5,9,90,92	1,10,122,124,125,1 26,142,148,159,197 ,2,201,246,247,248, 3,4,5,9,90,92	Acute and chronic tonsillitis,Acute bronchitis,Appendicitis and other appendiceal conditions,Bacterial infection; unspecified site,Fever of unknown origin,Gangrene,HIV infection,Immunizations and screening for infectious disease,Infective arthritis and osteomyelitis (except that caused by tuberculosis or sexually transmitted di,Inflammation; infection of eye (except

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				that caused by tuberculosis or sexually transmitteddisease),Intestinal infection,Lymphadenitis,Mycoses,Other upper respiratory infections,Otitis media and related conditions,Peritonitis and intestinal abscess,Pneumonia (except that caused by tuberculosis or sexually transmitted disease),Septicemia (except in labor),Sexually transmitted infections (not HIV or hepatitis),Skin and subcutaneous tissue infections,Tuberculosis,Urinary tract infections
	Influenza	123	123	Influenza
Musculoskeletal and integumentary	Musculosketal	197,198,199,200, 203,204,205,206, 207	173,198,199,200,20 3,204,205,206,207	Chronic ulcer of skin,Osteoarthritis,Osteoporosis,Other diagnostic procedures on skin subcutaneous tissue fascia and breast,Other inflammatory condition of skin,Other non-traumatic joint disorders,Other skin disorders,Pathological fracture,Skin and subcutaneous tissue infections,Spondylosis; intervertebral disc disorders; other back problems
	Connective	144,202,210,211, 253,54,57,86,87,8 8,89,91,94	144,202,210,211,25 3,54,57,86,87,88,89 ,91,94	Allergic reactions,Blindness and vision defects,Cataract,Glaucoma,Gout and other crystal arthropathies,Immunity disorders,Other connective tissue disease,Other ear and sense organ disorders,Other eye disorders,Regional enteritis and ulcerative colitis,Retinal detachments; defects; vascular occlusion; and retinopathy,Rheumatoid arthritis and related disease,Systemic lupus erythematosus and connective tissue

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				disorders
Neoplasm	Malignancy	12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,36,37,38,39,40,41,42,43,44,45,47	12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,36,37,38,39,40,41,42,43,44,45,47	Cancer of bladder,Cancer of bone and connective tissue,Cancer of breast,Cancer of bronchus; lung,Cancer of cervix,Cancer of colon,Cancer of esophagus,Cancer of kidney and renal pelvis,Cancer of liver and intrahepatic bile duct,Cancer of other female genital organs,Cancer of other GI organs; peritoneum,Cancer of other male genital organs,Cancer of other urinary organs,Cancer of ovary,Cancer of pancreas,Cancer of prostate,Cancer of rectum and anus,Cancer of stomach,Cancer of testis,Cancer of thyroid,Cancer of uterus,Cancer; other and unspecified primary,Cancer; other respiratory and intrathoracic, Hodgkin's disease,Leukemias,Maintenance chemotherapy; radiotherapy,Malignant neoplasm without specification of site,Melanomas of skin,Multiple myeloma,Neoplasms of unspecified nature or uncertain behavior, Non-Hodgkin's lymphoma,Other and unspecified benign neoplasm,Other non-epithelial cancer of skin,Secondary malignancies

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Women's health and perinatal care	Women's health and perinatal care	167,168,169,170, 171,172,173,174, 175,176,177,178, 179,180,181,182, 183,184,185,187, 188,189,190,191, 192,193,194,195, 196,218,220,221, 223,224,46	167,169,170,171,172,173,174,175,176, 177,178,179,180,181,182,184,185,187, 188,189,190,191,192,193,194,195,196, 218,219,220,221,223,224,46	Benign neoplasm of uterus,Birth trauma,Contraceptive and procreative management,Early or threatened labor,Ectopic pregnancy,Endometriosis,Female infertility,Fetal distress and abnormal forces of labor,Fetopelvic disproportion; obstruction,Forceps delivery,Hemorrhage during pregnancy; abruptio placenta; placenta previa,Hypertension complicating pregnancy; childbirth and the puerperium,Induced abortion,Inflammatory diseases of female pelvic organs,Intrauterine hypoxia and birth asphyxia,Liveborn,Malposition; malpresentation,Menopausal disorders,Menstrual disorders,Nonmalignant breast conditions,OB-related trauma to perineum and vulva,Other complications of birth; puerperium affecting management of mother,Other complications of pregnancy,Other female genital disorders,Other perinatal conditions,Other pregnancy and delivery including normal,Ovarian cyst,Polyhydramnios and other problems of amniotic cavity,Postabortion complications,Previous C-section,Prolapse of female genital organs,Prolonged pregnancy,Respiratory distress syndrome,Short gestation; low birth weight; and fetal growth retardation,Spontaneous abortion,Umbilical cord complication
Renal	Renal	156,157,158	156,157,158,161	Acute and unspecified renal

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				failure,Chronic kidney disease,Nephritis; nephrosis; renal sclerosis,Other diseases of kidney and ureters
Respiratory	Respiratory and hypoxia	103,127,128,129, 130,131,132,133, 134,56	103,127,128,129,13 0,131,132,133,134, 135,56	Aspiration pneumonitis; food/vomitus,Asthma,Chronic obstructive pulmonary disease and bronchiectasis,Cystic fibrosis,Intestinal infection,Lung disease due to external agents,Other lower respiratory disease,Other upper respiratory disease,Pleurisy; pneumothorax; pulmonary collapse,Pulmonary heart disease,Respiratory failure; insufficiency; arrest (adult)
Functional group				
Psychiatry	Psychiatry	650,651,652,656, 657,658,659,663, 670	650,651,652,656,65 7,658,659,670	Adjustment disorders,Anxiety disorders,Attention-deficit conduct and disruptive behavior disorders,Attention-deficit, conduct, and disruptive behavior disorders,Impulse control disorders NEC,Impulse control disorders, NEC,Miscellaneous mental health disorders,Mood disorders,Personality disorders,Schizophrenia and other psychotic disorders,Screening and history of mental health and substance abuse codes
Symptomatic and care	Symptomatic and care	246,252,254,255, 256,000,000,000	252,254,255,256,25 7,258,259	Administrative/social admission,Fever of unknown origin,Malaise and fatigue,Medical examination/evaluation,Other aftercare,Other screening for suspected conditions (not mental disorders or infectious disease),Rehabilitation care;

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				fitting of prostheses; and adjustment of devices,Residual codes; unclassified
Syncope	Syncope	245,93	245,93	Conditions associated with dizziness or vertigo,Syncope
Others	Iatrogenic	0,237,238,2616	237,238,2616	Adverse effects of medical care,Complication of device; implant or graft,Complications of surgical procedures or medical care,E Codes: Adverse effects of medical care,Invalid procedure
	Congenital	208,209,212,213,214,215,216,217,219,654,655	208,209,212,213,214,215,216,217,654,655	Acquired foot deformities,Cardiac and circulatory congenital anomalies,Developmental disorders,Digestive congenital anomalies,Disorders usually diagnosed in infancy childhood or adolescence,Disorders usually diagnosed in infancy, childhood, or adolescence,Genitourinary congenital anomalies,Nervous system congenital anomalies,Other acquired deformities,Other bone disease and musculoskeletal deformities,Other congenital anomalies,Short gestation; low birth weight; and fetal growth retardation
	Environment	2611	2611	E Codes: Natural/environment,External cause codes: Natural/environment

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ORIGINAL WORK

Incidence, Causes, and Prognostic Outcomes of Acute Coma: A Nationwide Population-Based Retrospective Cohort Study in Taiwan

ABSTRACT

Objectives: Identifying the underlying cause of acute coma is crucial for improving outcomes in this time-sensitive medical emergency. This study aims to investigate the clinical characteristics of acute coma.

Methods: This nationwide population-based retrospective cohort study used the Taiwan National Health Insurance Database to identify individuals with first-ever acute coma from 2000 to 2017 based on emergency department (ED) discharge diagnoses. AHRQ Clinical Classification Software (CCS) was employed to categorize acute coma into 23 clinical causes. We examined the characteristics of acute coma cases. We analyzed acute coma event rate, age-specific incidence rates, underlying causes, and clinical outcomes such as reversible coma, hospitalization, and 30-day mortality. We also evaluated one-year medical utilization and functional outcomes. Long-term factors influencing mortality were ascertained using Cox regression.

Participants: Among 99,217,322 ED visits between 2000 and 2017, 419,480 acute coma events were identified. Excluded ED visits with only acute coma

diagnosis code, lacking further information, and participants lacking sociodemographic data or with prior nursing home or disabled status, 205,747 cases remained in the final research cohort.

Results: The acute coma overall event rate is 4.23 per 1,000 ED visits. The overall incidence rate is 0.93 per 1,000 person-years. We analyzed 205,747 first-ever acute coma cases, predominantly male (58.90%), aged 58.27 years (SD 23.04). Infection and CNS causes were predominant. This study finds that 45.49% of cases are reversible, 41.66% require hospitalization, and the 30-day mortality group accounts for 12.85%. CNS and drug-related causes contributed to increased 30-day mortality, while psychiatric, alcohol, women's health and perinatal care, and seizure are causes linked to reversible coma. Patients needed intensive care (26.54%), life-sustaining treatments (41.09%), or disability (6.57%). Generalized estimating equations revealed that CNS (aOR, 0.68; 95% CI, 0.62 to 0.74; p < .0001) and drug-related causes (aOR, 0.72; 95% CI, 0.65 to 0.81; p < .0001) were less likely to result in reversible coma, suggesting higher 30-day mortality risk factors. Cox regression showed drugs (aHR, 1.30, 95% CI 1.20 to 1.41, p < .001), neoplasm (aHR, 1.18, 95% CI 1.11 to 1.25, p < .001), and symptoms causes (aHR, 1.44, 95% CI 1.24 to 1.67, p < .001) elevated the long-term death risk.

Conclusion: The most common causes of acute coma were infection and CNS-related etiologies. Meanwhile, CNS and drug-related were the most explained causes of mortality. Acute coma with diverse causes and significant impacts on clinical outcomes. Our study demonstrates the innovative use of ICD codes aggregation to CCS groups in acute coma clinical study, providing valuable insights into its clinical nature.

Keywords

Coma, Clinical Classifications Software, Incidence, Risk factors, Natural history studies, Prognosis

Search Terms

Clinical Neurology: Coma,

Epidemiology: Incidence studies,

Epidemiology: Risk factors in epidemiology,

Epidemiology: Natural history studies (prognosis),

Clinical Neurology: Prognosis

Coma, Clinical Classifications Software, Incidence, Risk factors, Natural history studies, Prognosis

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We utilized the AHRQ Clinical Classification Software (CCS) to develop a clinical research model for investigating acute coma and its clinical characteristics.

⇒ This is the first nationwide retrospective cohort study to utilize longitudinal data, offering insights into the clinical progression and mortality risk of first-ever acute coma.

⇒ The proposed research model enables international comparative studies of acute coma, advancing evidence-based practice and supporting the development of AI algorithms for coma management.

⇒ The absence of coma scale data to accurately define the first-ever acute coma cohort represents a limitation, potentially affecting the precision of acute coma incidence estimation.

⇒ Heterogeneity in the results may arise from variability in the classification of underlying mechanisms and causes of acute coma across differing definitions, datasets, and settings.

INTRODUCTION

Acute coma is a critical time-sensitive condition with heterogeneous causes that requires urgent attention and has significant impacts on patients and healthcare professionals.[1] It is characterized by profound failure of the neurological system responsible for maintaining arousal and awareness, leading to either a reflex response or no response to external stimuli at all.[2] Prior studies estimate that 1-5% of patients presenting to the emergency department (ED) have a disturbance in consciousness.[3 4] Emergency care researchers often categorize acute coma into three etiological factors: primary CNS disease, severe medical conditions that affect the CNS secondarily, or functional such as psychogenic disorder.[5 6] The clinical course of acute coma has been classified into three main categories: reversible coma, where patients recover quickly after ED management and can be discharged without any functional deficits; mortality group consisting of patients who do not survive their coma event despite medical interventions; and hospitalization group, which includes patients requiring hospitalization that may need intensive care or life-sustaining treatments (LSTs), or complicated with long-term disabilities.[7 8] Major challenge in studying acute coma is its heterogeneous nature, with multiple possible contributing factors often present in a single patient. Variations in acute coma

study results may arise due to differences in definitions, cause classifications, and follow-up periods.[9] These factors can affect outcomes and complicate direct comparisons between studies, underscoring the need for standardized methodologies.[10] Despite the urgent need for a better understanding clinical nature of acute coma, there is a lack of large-scale longitudinal studies that can comprehensively address the incidence, causes, clinical course, and outcomes of acute coma.

The Agency for Healthcare Research and Quality (AHRQ) has developed the Clinical Classification Software (CCS) to provide a standardized method for classifying diagnosis codes into CCS categories based on clinical characteristics.[11 12] The CCS categories employ the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Clinical Modification (ICD-10-CM) classification systems to aggregate large numbers of ICD diagnostic codes into 285 clinically meaningful categories, thereby making clinical research more feasible. Our study aims to (1) estimate acute coma incidence, (2) use the CCS to identify acute coma causes, and (3) investigate the clinical course and outcomes.

MATERIALS AND METHODS

Study design and setting

In this nationwide population-based retrospective cohort study, we utilized

Taiwan National Health Insurance Research Database (NHIRD) to examine ED visits between January 1, 2000, and December 31, 2017. The NHIRD, managed by the Ministry of Health and Welfare, offered a comprehensive dataset with information on demographics, comorbidities, hospitalization, functional status, and mortality. This study was conducted with the approval of the local ethics board and involved no direct patient interaction. We carried out a retrospective analysis of claims data, ensuring all personal identifiers were encrypted to uphold patient confidentiality.

Acute coma participants' definition

Given the nature of this study, we utilized the NHIRD dataset to investigate acute coma incidences. However, the NHIRD dataset lacks specific indicators, such as the Glasgow Coma Scale (GCS), to accurately represent coma status. Consequently, we relied on the judgment of emergency physicians in diagnosing acute coma instances, especially in cases where there was no explicit diagnosis but an indication of coma in the ED's diagnoses. We employed DynaMed (2020) Coma International Classification of Diseases (ICD) codes to define acute coma objectively.[13] These codes encompass a range of acute coma conditions, including "780.1" and "780.01" for comatose, "780.09" for other alterations of consciousness, "R40.0" for somnolence, "R40.1" for stupor, "R40.2" for unspecified coma, and "S06.7" for intracranial injury-related

coma. Therefore, our study population consisted of cases that included any of these codes within the three diagnoses upon ED discharge records and remained as the final research cohort (Figure 1). The present study implemented several exclusion criteria to ensure precise estimation of the cause, disease progression, and clinical outcomes associated with acute coma. First, we omitted cases lacking comprehensive sociodemographic data. Second, we excluded those who were undergoing life-sustaining treatments or were disabled or residing in a nursing home prior to the first-ever acute coma event. Additionally, cases diagnosed with acute coma in the ED that the CCS could not further classify due to the absence of additional diagnostic information from the ED or inpatient records were excluded from the study. To rule out hospitalizations potentially unrelated to the acute coma events, we excluded samples in which hospitalization occurred more than 14 days after the acute coma index date.

Incidence estimates

We estimated the annual acute coma event rate from 2000 to 2017, with acute coma events as the unit of analysis. The event rate of acute coma is calculated by dividing the number of events by ED visits. In addition, we determined crude age group-stratified incidence rates were determined per 1000 person-years, with denominators based on the number of insured individuals during the year,

taking into account their survival status and the person-years they contributed within that year. Considering insured individuals' survival status and person-years contributed and reported age-specific incidence rates in pediatric (1-18), adult (19-64), and senior adult (65+) groups with corresponding summary statistics.

Clinical course, causes, and outcomes assessment

The study explored the clinical course of acute coma using each patient's first-ever event as the unit of analysis. The index date was set as the date of the first diagnosis of acute coma. ED visits were categorized into reversible coma, hospitalization, and 30-day mortality.[14] Individuals who died within 30 days of the acute coma ED index date were classified as the 30-day mortality group. Those requiring hospitalization within seven days post-episode but not dying within 30 days constituted the hospitalization group. Patients diagnosed with acute coma in the ED without needing hospitalization or facing death were categorized as the reversible coma group.

Using CCS methodology,[12 15 16] we categorized ICD codes from death or hospitalization into 23 acute coma causes (Supplementary Table 1) and a statistical analysis plan is available in the (Supplementary Program). The diagnosis sequence begins with death, hospitalization, and ED diagnosis if no death or hospitalization occurs. These causes were further classified into three

etiological mechanisms: (1) primary CNS diseases (neurological etiology), (2) medical conditions affecting the CNS secondarily (medical etiology), and (3) functional etiology.[5] Neurological etiology included acute CNS insult, chronic neurodegenerative encephalopathy, paroxysmal seizure disorders, and brain trauma. Medical etiology included alcohol-related coma, drugs, and organ system dysfunction. Functional factors included psychogenic disorders, symptoms, syncope, and other related causes. Patients were followed for one year to evaluate short-term outcomes (30-day mortality or reversible course) and long-term outcomes (ICU admission, LSTs,[17] rehabilitation, disability status, or nursing home residency).

Statistical analysis

We used χ^2 tests to analyze baseline categorical characteristics and compared continuous variables' mean among coma groups with One-Way ANOVA. Generalized estimating equations (GEE) were used to estimate acute coma's adjusted odds ratio (aOR), accounting for multiple causes and covariates like sex, age, Charlson Comorbidity Index (CCI), occupation, urbanization, and income. Survival analysis was conducted for reversible and hospitalization groups, tracking survival probability and calculating time to event (death) or censoring. Cox regression investigated potential causes of death events, with hazard ratios identifying factors affecting long-term outcomes. Analyses were

performed with SAS software, version 9.4, and a significance level of $p < 0.05$.

RESULTS

Cohort characteristics and clinical course estimate

Among 99,217,322 ED visits between 2000 and 2017, 419,480 acute coma events were identified. Of these, 365,675 patients were discharged or hospitalized within seven days. After excluding 4,385 ED visits with only acute coma diagnosis code, lacking further information, and participants lacking sociodemographic data or with prior nursing home or disabled status, 205,747 cases remained in the final research cohort (Figure 1). The cohort clinical course classified 93,598 (45.49%) as reversible acute coma group, 85,712 (41.66%) as hospitalization group, and 26,437 (12.85%) as 30-day mortality group. The study population was 54.39% male, with an average age of 58.27 (SD 23.04) years (Supplementary Table 2).

Incidence of acute coma

Table 1 analyzes ICD diagnosis codes for acute coma events, revealing: (1) a crude event rate of 4.23 per 1,000 ED visits, (2) an average overall incidence rate of 0.93 per 1,000 person-years, and (3) age-specific incidence rates, 0.13 for pediatric, 0.57 for middle-aged, and 7.13 for senior adult groups. A significant mean decrease in incidence rate in 2016 suggests that age and temporal factors may influence acute coma incidence.

Causes and outcomes of acute coma

Supplementary Table 1 presents leading acute coma causes, including infection (15.10%), CNS (14.61%), digestive (9.67%), cardiovascular (9.41%), and trauma-related (8.65%). Common reversible causes included infection (15.72%), trauma (10.89%), digestive (10.00%), women's health and perinatal care (9.56%), and CNS (8.74%). Hospitalization for acute coma frequently resulted from CNS (17.08%), infection (16.34%), cardiovascular (9.51%), digestive (9.30%), and diabetes and insulin (6.45%). Leading causes of death were CNS (27.40%), cardiovascular (12.41%), digestive (9.73%), trauma (9.10%), and infection (8.87%). Medical etiologies were the primary factor (66.75%), with neurological (27.60%) and functional (5.65%) etiologies also contributing. Short-term outcomes indicated 45.49% of cases left the ED without sequelae, 12.85% experienced 30-day mortality, and 41.66% necessitated hospitalization within seven days. Elderly patients had a significantly higher mortality rate of 62.56% compared to 11.56% for younger patients. The one-year follow-up showed ICU treatment (26.54%), LSTs (41.09%), rehabilitation (14.23%), disability (6.57%), and nursing care (1.88%).

Multivariate analysis of acute coma

The GEE analysis identified covariates significantly associated with increased acute coma mortality, including females, older age, higher CCI

scores, low income, and rural residence (Supplementary Table 3). Compared to other causes, CNS (adjusted odds ratio [aOR], 0.68; 95% CI: 0.62 to 0.74; p < .0001) and drug-related causes (aOR, 0.72; 95% CI: 0.65 to 0.81; p < .0001) had lower odds of reversible coma compared to 30-day mortality, while psychiatric (aOR, 57.02; 95% CI: 34.11 to 95.33; p < .0001), alcohol (aOR, 33.8; 95% CI: 21.81 to 52.38; p < .0001), women's health and perinatal care (aOR, 11.86; 95% CI: 10.11 to 13.92; p < .0001), seizures (aOR, 8.32; 95% CI: 6.15 to 11.24; p < .0001), and musculoskeletal/integumentary causes (aOR, 8.16; 95% CI: 7.04 to 9.47; p < .0001) had higher odds. Drug causes had lower odds of hospitalization compared to mortality (aOR, 0.82; 95% CI: 0.73 to 0.91; p=.0003), while psychiatry (aOR, 48.29; 95% CI: 28.88 to 80.77; p < .0001), seizure (aOR, 9.01; 95% CI: 6.67 to 12.17; p < .0001), women's health and perinatal care (aOR, 5.44; 95% CI: 4.63 to 6.40; p < .0001), and alcohol (aOR, 5.20; 95% CI: 3.31 to 8.17; p < .0001) causes increased the odds. Compared to functional etiology, neurological etiology had lower odds of reversible coma (aOR, 0.55; 95% CI, 0.51 to 0.59, p < .0001) and hospitalization (aOR, 0.70; 95% CI 0.65 to 0.75, p < .0001), while medical etiology had higher odds of reversible coma (aOR, 1.39; 95% CI: 1.30 to 1.49, p < .0001) and hospitalization (aOR, 1.16; 95% CI: 1.09 to 1.25, p < .0001).

The Kaplan-Meier estimation (Supplementary Figure 1) and Cox proportional hazards regression (Table 2) revealed increased mortality risk associated with higher CCI score (adjusted hazard ratios [aHR], 1.08, 95% CI 1.07 to 1.09, p < .001), older age (aHR, 2.17, 95% CI 2.13 to 2.22, p < .001), manual labor (aHR, 1.03, 95% CI 1.02 to 1.04, p < .001), drug (aHR, 1.30, 95% CI 1.20 to 1.41, p < .001), neoplasm (aHR, 1.18, 95% CI 1.11 to 1.25, p < .001), and symptoms cause (aHR, 1.44, 95% CI 1.24 to 1.67, p < .001). In addition, the average mortality post-acute coma for the reversible group was observed at 7.10 years, while for the hospitalization group, it occurred at 6.41 years.

Sensitivity test of acute coma

To assess the robustness of our findings, we focused on the definition of an acute coma cohort, explicitly examining the first-ever episode that led to hospitalization within either a 7-day or 14-day period. Our analysis revealed no significant differences between these two cohort definitions in terms of clinical course subgroup distribution and cause classification for acute coma (see Supplementary Table 4). This suggests that our findings are consistent and reliable across different definitions.

DISCUSSION

Acute coma frequently represents a common pathway of organ dysfunction

from diverse causes, significantly impacting patients' survival and quality of life and straining healthcare resources. This study aims to explore the incidence density, causes, clinical courses, and outcomes of acute coma. Several methodological and result issues warrant discussion.

Methodology discussion

Our 18-year longitudinal retrospective cohort study employs the ICD coding system and the Clinical Classification Software (CCS) method to address the complexity of acute coma's causes and etiologies. This complexity, driven by a wide range of reversible and time-sensitive factors, poses significant challenges in synthesizing diverse clinical causes into a unified cohort for claims-based research. Previous studies have often relied on medical record reviews[18] or rigorously designed cohort studies,[19] lacking a comprehensive and longitudinal perspective. To bridge this research gap, we devised an innovative clinical research model integrating big data analytics with clinical investigation. This approach offers a novel framework for examining the multifaceted clinical scenarios related to acute coma through claims-based data, thereby opening new avenues for neuroscientific research and enhancing emergency medical decision-making systems.

Study design, population, and cohort definition

The Taiwan NHIRD, encompassing the entire population and offering

comprehensive medical services, facilitated a thorough analysis of acute coma's clinical nature. Besides, The large cohort of over 200,000 patients offered a robust population representation. Moreover, we defined the cohort based on one impaired consciousness in the ED study, where the average hospitalization duration was 6.4 days. Therefore, we included cases where the onset of acute coma and subsequent hospitalization occurred within seven days as part of the study cohort.[20] By excluding patients with prior nursing home residence or disability status it provides a better understanding of the true incidence and outcomes of first-ever acute coma.

Meanwhile, the lack of clinical coma scale data raises concerns about the accuracy of the methodology, which relies on ICD coding and the CCS method. Our study adopted a broader definition of acute coma, using ICD codes, covering various alterations of consciousness such as somnolence, stupor, unspecified coma, and intracranial injury-related coma. Our study adopted a broad range of acute coma diagnosis codes to capture various clinical scenarios.[21] We used ICD coding methodology covering the qualitative spectrum of 'decreased consciousness,' including somnolence, stupor, coma, and quantitative GCS score ranges [21]. We also included the current quantitative approach to coma assessment, coding GCS scores of 13-15 as R40.0

(somnolence), 9-12 as R40.1 (stupor), and ≤ 8 as R40.2 (coma, unspecified). This approach ensured a thorough representation of acute coma in our research sample.

Defined of acute coma causes

Integrating CCS with the ICD coding system in clinical research potentially offers a holistic and nuanced methodology for categorizing complex clinical data into clinically meaningful classes.[15] While established frameworks for transforming a myriad of ICD codes into clinically relevant categories that can guide clinical decision-making, inform policy interventions, or enable regular monitoring are not yet widespread,[12] In our study, we utilized CCS to condense 285 CCS categories into 23 clinically relevant causes of acute coma, rendering the study practically feasible and enabling the in-depth analysis of acute coma's multifaceted clinical manifestations. This approach facilitates large-scale, longitudinal, population-based studies in EDs, optimizing approaches to address acute coma's clinical nature.

Results discussion

Understanding the clinical characteristics of acute coma makes it crucial for intensivist clinicians to identify the cause to prevent disability[22] and emergency medical policy applications.

Causes, clinical courses, and outcomes

Infections, CNS disorders, digestive issues, cardiovascular events, and trauma

are leading causes of acute coma. Our research results are consistent with international findings, with infection being the most common cause.[23 24] Acute coma causes differ based on geography[25] or age.[23] For instance, poisoning contributes to approximately one-third of unconsciousness cases in Nordic countries.[25] In children, common causes are intoxication, epilepsy, infection, and traumatic brain injury.[18] CNS and infectious disorders are more common in adults and older adults.[18 21] The prominence of digestive causes for acute coma in our cohort may be due to the prevalence of hepatitis and hepatocellular carcinoma in Taiwan.[26] To facilitate a broader understanding of public health implications related to the potential etiologies and mechanisms underlying acute coma, and to enable meaningful comparisons with existing literature, we have classified the etiologies of acute coma into three major categories: neurological, medical, and functional factors.[5 6 27] This categorization approach aids in developing targeted intervention strategies and informs policy-making. Neurological causes account for about one-third of cases, while non-neurological causes comprise the remaining two-thirds.[28] Schmidt (2017) reported that neurological and medical etiologies each contributed to about 50% of acute coma cases.[5] Functional or psychogenic coma constituted around 5% of cases. It is worth further exploring the causes of coma

resulting from functional factors.

The clinical course of acute coma varies due to differing underlying causes or etiologies.[9] [23] Over half of the first-ever acute coma patients required hospitalization or faced mortality. In contrast, the other nearly half demonstrated reversible outcomes. The short-term in-hospital mortality rate for patients with acute coma is about 5 -11%[3] [20] [29] with longer follow-up reaching 25%.[29] Our study found that 27.60% of acute coma cases were attributed to neurological etiology, and within the mortality group, 38.16% of cases had a neurological cause. This supports prior research indicating that clinical course is highly dependent on etiology.[23] Syncope and seizures are generally believed to be the most common causes of reversible coma. However, in our study, these two common causes accounted for only 1.33% of cases of overall acute coma. This may support researchers' definition of coma as a state of prolonged sustained unconsciousness lasting at least one hour.[30] Our emergency physicians may better understand syncope and seizure, improving diagnostic accuracy.[31] Study showed that twenty percent of patients with acute coma may have already been reversible on admission.[29] If these patients are monitored for two months after hospitalization, one-third of them may fully recover consciousness.[32] Our study found that approximately 45.49% of patients had reversible coma. The higher

proportion of reversible coma in our study may reflect a more lenient coding of coma or the higher quality of emergency medical care by emergency physicians in our study. These results suggest that the outcome of acute coma is highly dependent on the underlying cause and severity of the condition.[33] Regarding long-term outcomes, one-quarter of patients with first-ever acute coma necessitated ICU admission, and forty percent required LSTs within one year. The high percentage of patients in the LSTs group who require long-term care and have a high mortality rate, emphasizes the need for improved management strategies for patients with acute coma.[7]

Incidence

Our study found an acute coma event rate of 4.23 visits per 1,000 ED visits, consistent with the Schmidt et al. (2019) ED cohort study.[29] However, our results differ from those of another study that reported 0.29-0.40 cases of coma per 1,000 ED visits.[34] Based on the ICD code approach, studies suggested that acute coma is about 0.93-5% of all ED visits.[28 35]. Pediatric non-trauma coma studies also have reported incidences ranging from 0.3 to 1.6 per 1,000 person-years.[23] This disparity in results may be attributed to differences in research questions, study design, study population, or definitions.[36]

We investigated the incidence rates of acute coma in different age groups and temporal trends. The highest incidence rate of acute coma was observed

in the elderly age group, emphasizing the significance of this public health concern in the aging population. However, there is also some variability in the incidence rates over time. We found that the incidence rate stabilized at around 1 per 1,000 person-years from 2007 to 2015 and observed a significant mean decrease in the incidence rate in 2016 compared to previous years. Specifically, there was a significant mean decrease from 0.73 per 1,000 person-years in 2016 to 0.63 per 1,000 person-years in 2017. One possible explanation for reducing acute coma incidence during 2016-2017 is the transition from the ICD-9 to the ICD-10 coding system in 2015. We also found no significant difference in ED visits between 2014 and 2017 (5,904,262 vs 5,945,444, respectively). Thus, the substantial change in acute coma incidence could be an artifact of the ICD coding transition effect.[37]

Strengths and Limitations

This study has several strengths and limitations. Strengths include using nationwide longitudinal data to observe first-ever acute coma patterns, enabling tracking of clinical progression. The average post-acute coma mortality occurring seven years highlights its importance as a risk factor and common pathway for mortality. Additionally, the study employed AHRQ CCS methodology, facilitating regular monitoring of acute coma clinical information and enabling tailored intervention plans.

The present study has several limitations that need to be acknowledged. Firstly, the absence of a coma scale to accurately define the first-ever acute coma cohort represents a significant limitation. Instead, the study relied on acute coma-related diagnoses coded by emergency physicians in the ED, potentially leading to an underestimation of acute coma incidence and compromising the accuracy of identifying the causes of coma. Additionally, the conversion between ICD-9 and ICD-10 coding systems may introduce inaccuracies in estimating coma-related diagnoses due to potential discrepancies and inconsistencies in classification. Consequently, the reliability of the results may be affected. Furthermore, it is important to recognize that the acute coma diagnosis employed in this study may not fully capture the underlying causes or medical utilization, as multiple contributing pathologies could be involved due to potential multiple underlying pathologies.[29] The complexity of coma etiology and the potential presence of various underlying factors may limit the accuracy of attributing the diagnosis to a single cause. Moreover, a small proportion (about 2%) of acute coma patients presented in the ED lacked further diagnostic information, which reflects the challenge in diagnosing cases of coma with unknown origins and introduces potential uncertainty and incomplete data in the analysis. Another limitation is the

reliance on data limited to the year 2017, preventing examining the potential effects of the COVID-19 pandemic. Incorporating the impact of the pandemic would have enhanced the understanding of the significance of infections and central nervous system-related causes in estimating acute coma incidence. Finally, it should be noted that this study did not utilize the World Health Organization's (WHO) World Standard Population for age-specific rates adjustment, which may limit the generalizability and comparability of the findings with other studies that utilize standardized rates based on the WHO standard populations. These limitations should be considered when interpreting the study's results, and future research should address these limitations to enhance the robustness and applicability of the findings.

CONCLUSION

Acute coma often represents a common pathway of organ dysfunction with diverse causes or etiologies, significantly impacting mortality and disability. Our study demonstrates the innovative use of ICD codes aggregation to CCS groups in acute coma clinical study, providing valuable insights into its clinical nature. This research model has the potential to facilitate international comparative studies of acute coma characteristics using healthcare databases.

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Contributorship statement

Contributorship statement CY Lin took a lead role in conceptualizing the study and writing the original draft, and was responsible for formal data analysis. ML Chang verified the underlying data in the manuscript. MC Tsai contributed to study design, data curation, and formal data analysis and was responsible for data collection. JF Liang and ML Chang ensured accurate data analysis and interpretation and verified the manuscript's underlying data. CC Liu, YC Lee and ML Chang supervised the study, validated the results, and significantly contributed to reviewing and editing the manuscript. All authors participated in developing the study concept and design, analyzing and interpreting data, and preparing the manuscript. We have all approved the final manuscript and agree to be accountable for all aspects of the work, promising to appropriately

investigate and resolve any question related to the work's accuracy or integrity.

ML Chang acted as guarantor.

Source of support

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Patients or the public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Declarations

1) **Confirm the manuscript complies with all instructions to the authors**

   The authors confirm that our manuscript adheres to all the instructions provided for authors.

2) **Confirm that authorship requirements (see below) have been met and the final manuscript was approved by all authors**

   All authors, coinvestigators, and contributors know and agree to the Authorship Policies outlined in the Author Center.

3) **Confirm that this manuscript has not been published elsewhere and is not under consideration by another journal**

   The authors confirm that this work is original, unpublished elsewhere and respectfully request its consideration for acceptance in the esteemed journal.

4) **Confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate (see**

below). Retrospective studies require a statement regarding IRB approval

All authors have completed the ICMJE conflict of interest form and declare no conflicts of interest in relation to this manuscript. The study involved a retrospective analysis of encrypted unique personal identification data without direct patient involvement. Therefore, no patient consent was necessary for the completion of this study. As the corresponding author, I confirm that we complied with all applicable laws regarding data protection and privacy. No patients were involved. This study was a retrospective claim data analysis that included all encrypted unique personal identification. Ethics approval: IRB of Taipei City Hospital, number-TCHIRB-10807003-E.

5) **Disclose Conflicts of Interest for all authors**

The authors report no disclosures relevant to the manuscript.

6) **Confirm the use of reporting checklist (see below), if appropriate**

The authors have confirmed the use of reporting checklists. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement when reporting observational studies and the Standards of Reporting of Neurological Disorders (STROND) for reporting incidence studies in neuroepidemiology.

Data Availability Statement

Taiwan National Health Insurance Research Database, which was provided by the National Health Insurance Administration, and is managed by National Health Research Institutes.

Table and Figure Titles

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Table 2 Multivariate Cox regression analysis of factors contributing to all-cause mortality in acute coma patients

Supplementary Figure 1 Survival analysis of acute coma patients
Supplementary Table 1 Clinical classification software for grouping the causes of acute coma
Supplementary Table 2 Characteristics of acute coma cohort
Supplementary Table 3 Generalized linear model analysis of acute coma patients
Supplementary Table 4 Characteristics of acute coma hospitalization within 14 days cohort
Supplementary statistical analysis plan SAS program using clinical classification

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Table 1 Acute coma event rate and incidence by year and age group

Year	ED visits	Coma events	Coma rate (‰)	Incidence (‰) (95% CI)	Age 1-18 Incidence (‰) (95% CI)	Age 19-64 Incidence (‰) (95% CI)	Age ≧ 65 Incidence (‰) (95% CI)
2000	4,519,482	10,330	2·29	0·45 (0·44-0·46)	0·08 (0·08-0·09)	0·30 (0·30-0·31)	7·74 (7·53-7·95)
2001	4,707,002	11,480	2·44	0·49 (0·48-0·50)	0·09 (0·08-0·10)	0·32 (0·32-0·33)	7·77 (7·57-7·97)
2002	5,028,446	12,567	2·50	0·53 (0·52-0·54)	0·10 (0·09-0·11)	0·34 (0·33-0·34)	7·78 (7·59-7·97)
2003	4,776,136	13,246	2·77	0·56 (0·55-0·57)	0·10 (0·09-0·10)	0·36 (0·35-0·36)	7·21 (7·04-7·38)
2004	5,354,185	16,072	3·00	0·67 (0·66-0·68)	0·11 (0·10-0·11)	0·44 (0·43-0·45)	7·58 (7·41-7·74)
2005	5,416,581	20,535	3·79	0·85 (0·83-0·86)	0·12 (0·11-0·13)	0·56 (0·54-0·57)	8·80 (8·63-8·97)
2006	5,171,689	21,769	4·21	0·89 (0·88-0·90)	0·13 (0·12-0·13)	0·57 (0·56-0·58)	8·59 (8·43-8·75)
2007	5,282,870	23,591	4·47	0·96 (0·94-0·97)	0·13 (0·12-0·14)	0·58 (0·57-0·60)	8·74 (8·59-8·89)
2008	5,191,529	25,548	4·92	1·02 (1·01-1·04)	0·14 (0·13-0·15)	0·63 (0·62-0·64)	8·53 (8·39-8·67)
2009	5,770,750	27,062	4·69	1·08 (1·07-1·09)	0·15 (0·14-0·16)	0·65 (0·64-0·67)	8·43 (8·30-8·57)
2010	5,878,033	31,184	5·31	1·23 (1·22-1·25)	0·17 (0·16-0·18)	0·73 (0·71-0·74)	9·27 (9·13-9·41)
2011	6,060,366	33,944	5·60	1·33 (1·32-1·35)	0·19 (0·18-0·20)	0·80 (0·78-0·81)	9·24 (9·11-9·37)
2012	6,098,194	34,259	5·62	1·33 (1·32-1·34)	0·19 (0·18-0·20)	0·79 (0·78-0·80)	8·60 (8·47-8·72)
2013	5,753,114	33,531	5·83	1·29 (1·28-1·31)	0·20 (0·19-0·21)	0·76 (0·75-0·77)	7·80 (7·69-7·91)
2014	5,904,262	34,917	5·91	1·34 (1·32-1·35)	0·19 (0·18-0·21)	0·78 (0·77-0·79)	7·48 (7·38-7·59)
2015	6,055,577	33,366	5·51	1·27 (1·25-1·28)	0·21 (0·19-0·22)	0·73 (0·72-0·74)	6·57 (6·47-6·66)
2016	6,303,662	19,355	3·07	0·73 (0·72-0·74)	0·09 (0·09-0·10)	0·39 (0·38-0·40)	3·70 (3·63-3·76)
2017	5,945,444	16,724	2·81	0·63 (0·62-0·64)	0·07 (0·07-0·08)	0·33 (0·32-0·34)	2·96 (2·90-3·02)
Total	99,217,322	419,480					
Average			4·23	0·93 (0·93-0·94)	0·13 (0·13-0·13)	0·57 (0·57-0·57)	7·13 (7·10-7·16)

CI: confidence interval; ED: emergency department;

Coma rate(‰)=acute coma events/1,000ED visits

Incidence of acute coma per 1,000 person-year

Table 2 Multivariate Cox regression analysis of factors contributing to all-cause mortality in acute coma patients

	Cox proportional hazards	
	aHR	*p*-value
Sex (male)	0·82 (0·80 - 0·84)	< 0·001
CCI (CCI>1)	1·08 (1·07 - 1·09)	< 0·001
Age (old age)	2·17 (2·13 – 2·22)	< 0·001
Income (high)	0·98 (0·97 - 1·00)	0·05
Occupation (manual)	1·03 (1·02 - 1·04)	< 0·001
Area (urban)	1·02 (1·01 - 1·04)	0·01
Neurological group		
CNS	0·83 (0·79 - 0·88)	< 0·001
Encephalopathy	0·93 (0·87 - 0·99)	0·04
Seizure	0·32 (0·26 - 0·39)	< 0·001
Trauma	0·48 (0·45 - 0·52)	< 0·001
Medical group		
Alcohol	0·39 (0·30 – 0·51)	< 0·001
Cardiovascular	0·94 (0·89 - 0·99)	0·02
Digestive	0·91 (0·86 - 0·96)	< 0·001
Drugs	1·30 (1·20 - 1·41)	< 0·001
Electrolyte	0·99 (0·78 - 1·25)	0·93
Endocrine	0·76 (0·67 - 0·86)	< 0·001
Genitourinary	0·43 (0·38 – 0·49)	< 0·001
Hematology	0·63 (0·49 - 0·80)	< 0·001
Infection	0·66 (0·63 - 0·69)	< 0·001
Musculoskeletal and integumentary	0·31 (0·28 - 0·35)	< 0·001
Neoplasm	1·18 (1·11 - 1·25)	< 0·001
Renal	1·05 (0·97 - 1·13)	0·21
Respiratory	0·80 (0·75 - 0·85)	< 0·001
Women's health and perinatal care	0·15 (0·13 - 0·18)	< 0·001
Functional group		
Psychiatry	0·05 (0·03 - 0·05)	< 0·001
Symptoms	1·44 (1·24 – 1·67)	< 0·001
Syncope	0·00	.
Others	0·47 (0·42 - 0·53)	< 0·001

Age (old age group), CCI (CCI>1 group), Income (high-income group), Area (urban), Occupation (manual), Sex (male)

Syncope: no convergence

Figure 1 Flow diagram of the study

STROBE Statement

—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8-9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	

		Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	13

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed	8-9

		eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	11
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*9*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	11-13
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-18

Generalisability	21	Discuss the generalisability (external validity) of the study results	14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article	☒ **None**	
		We thank the Center for Public Health, Department of Education and Research, Taipei City Hospital, for providing administrative and research grant support.	
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2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None** The research grant supported by Taipei City Hospital	
3	Royalties or licenses	☒ **None**	
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	nal events		
6	Payment for expert testimony	☒ **None**	
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8	Patents planned, issued or pending	☐ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

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11	Stock or stock options	☒ **None**	
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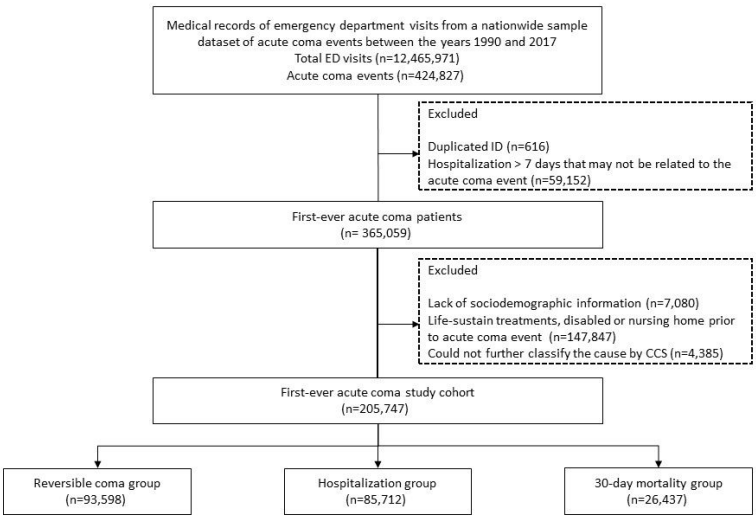
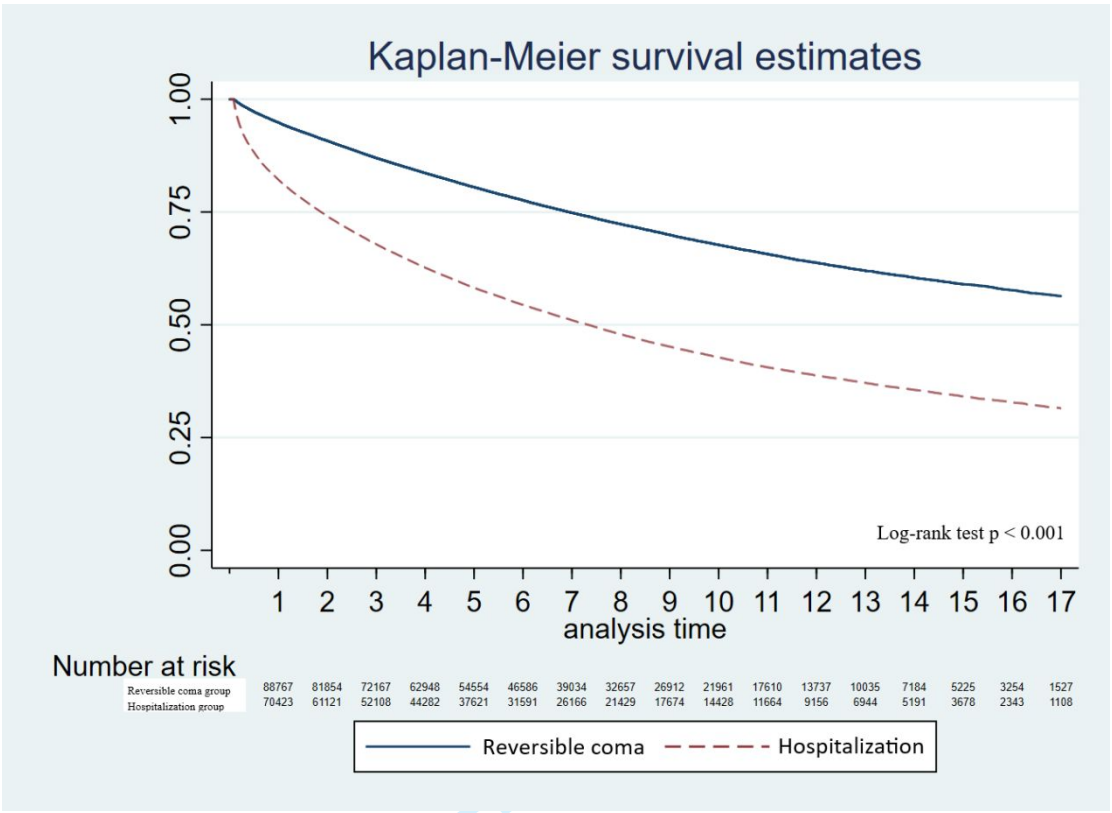


Figure 1 Flow diagram of the study



Supplementary Figure 1 Survival analysis of acute coma patients

Supplementary Table 1 Clinical classification software for grouping the causes of acute coma

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Neurological group				
Primary CNS	CNS meningitis	7,76	7,76	Meningitis (except that caused by tuberculosis or sexually transmitted disease),Viral infection
	Brain space occupied	11,35	11,35	Cancer of brain and nervous system,Cancer of head and neck
	CNS encephalitis	77,78,8	77,78,8	Encephalitis (except that caused by tuberculosis or sexually transmitted disease),Other CNS infection and poliomyelitis,Other infections; including parasitic
	Cerebrovascular disease	109,110,111,112,113,82	109,110,111,112,113,82	Acute cerebrovascular disease,Late effects of cerebrovascular disease,Occlusion or stenosis of precerebral arteries,Other and ill-defined cerebrovascular disease,Paralysis,Transient cerebral ischemia
	CNS trauma	227,228,233,234,235	227,228,233,234,235	Crushing injury or internal injury,Intracranial injury,Open wounds of head; neck; and trunk,Skull and face fractures,Spinal cord injury
Encephalopathy	Encephalopathy	79,80,81,84,95	79,80,81,84,95	Headache; including migraine,Multiple sclerosis,Other hereditary and degenerative nervous system conditions,Other nervous system disorders, Parkinson's disease
	Dementia	653	653	Delirium dementia and amnestic and other cognitive disorders,Delirium, dementia, and amnestic and other cognitive disorders
Seizure	Seizure and epilepsy	83	83	Epilepsy; convulsions

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Trauma	Trauma	225,226,229,230,231,232,236,239,240,244,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2612,2618,2619,2620,2621	0,144,145,146,147,148,149,225,226,229,230,231,232,236,239,240,244,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2612,2614,2618,2619,2620,2621	Arthroscopy,Burns,E Codes: Cut/pierceb,E Codes: Drowning/submersion,E Codes: Fall,E Codes: Fire/burn,E Codes: Firearm,E Codes: Machinery,E Codes: Motor vehicle traffic (MVT),E Codes: Other specified and classifiable,E Codes: Other specified; NEC,E Codes: Overexertion,E Codes: Pedal cyclist; not MVT,E Codes: Pedestrian; not MVT,E Codes: Place of occurrence,E Codes: Transport; not MVT,E Codes: Unspecified,External cause codes: Cut/pierce,External cause codes: Drowning/submersion,External cause codes: Fall,External cause codes: Fire/burn,External cause codes: Firearm,External cause codes: Machinery,External cause codes: Motor vehicle traffic (MVT),External cause codes: Other specified and classifiable,External cause codes: Other specified; NEC,External cause codes: Overexertion,External cause codes: Pedal cyclist; not MVT,External cause codes: Pedestrian; not MVT,External cause codes: Place of occurrence,External cause codes: Struck by; against,External cause codes: Transport; not MVT,External cause codes: Unspecified,Fracture of lower limb,Fracture of neck of femur (hip),Fracture of upper limb,Fracture treatment including reposition with or without fixation of other fracture or or dislocation,Fracture treatment including reposition with or without fixation; facial

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				fracture or dislocation,Fracture treatment including reposition with or without fixation; hip or femur fracture or dislocati,Fracture treatment including reposition with or without fixation; lower extremity fracture or disloc,Fracture treatment including reposition with or without fixation; radius or ulna fracture or disloca,Joint disorders and dislocations; trauma-related,Open wounds of extremities,Other fractures,Other injuries and conditions due to external causes,Sprains and strains,Superficial injury; contusion
	Injury and suicide	2615,662	2615,662	E Codes: Suffocation,External cause codes: Suffocation,Suicide and intentional self-inflicted injury
Medical group				
Alcohol	Alcohol	660	660	Alcohol-related disorders
Cardiovascular	Cardiovascular	100,101,102,104,105,106,107,108,114,115,116,117,118,119,121,247,96,97,98,99	100,101,102,104,105,106,107,108,114,115,116,117,118,119,121,183,96,97,98,99	Acute myocardial infarction,Aortic and peripheral arterial embolism or thrombosis,Aortic; peripheral; and visceral artery aneurysms,Cardiac arrest and ventricular fibrillation,Cardiac dysrhythmias,Conduction disorders,Congestive heart failure; nonhypertensive,Coronary atherosclerosis and other heart disease,Essential hypertension,Heart valve disorders,Hypertension complicating pregnancy; childbirth and the puerperium,Hypertension with complications and secondary hypertension,Lymphadenitis,Nonspecific chest pain,Other and ill-defined heart disease,Other circulatory disease,Other

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				diseases of veins and lymphatics,Peri-; endo-; and myocarditis; cardiomyopathy (except that caused by tuberculosis or sexually transm,Peripheral and visceral atherosclerosis,Phlebitis; thrombophlebitis and thromboembolism,Varicose veins of lower extremity
	Shock	249	249	Shock
Diabetes and insulin	Diabetes and insulin	186,49,50	186,49,50	Diabetes mellitus with complications,Diabetes mellitus without complication,Diabetes or abnormal glucose tolerance complicating pregnancy; childbirth; or the puerperium
Digestive	Digestive	120,136,137,138,139,140,141,143,145,146,147,152,153,154,155,250,251	120,136,137,138,139,140,141,143,145,146,147,152,153,154,155,250,251	Abdominal hernia,Abdominal pain,Anal and rectal conditions,Diseases of mouth; excluding dental,Disorders of teeth and jaw,Diverticulosis and diverticulitis,Esophageal disorders,Gastritis and duodenitis,Gastroduodenal ulcer (except hemorrhage),Gastrointestinal hemorrhage,Hemorrhoids,Intestinal obstruction without hernia,Nausea and vomiting,Noninfectious gastroenteritis,Other disorders of stomach and duodenum,Other gastrointestinal disorders,Pancreatic disorders (not diabetes)
	Liver	149,151,222,6	149,151,222,6	Biliary tract disease,Hemolytic jaundice and perinatal jaundice,Hepatitis,Other liver diseases
Drugs	Intoxication	241,242,243,2613,661	241,242,243,2613,661,663	E Codes: Poisoning,External cause codes: Poisoning,Poisoning by nonmedicinal substances,Poisoning by other medications and drugs,Poisoning by

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				psychotropic agents,Screening and history of mental health and substance abuse codes,Substance-related disorders
	Medication	2617	2617	Adverse effects of medical drugs,E Codes: Adverse effects of medical drugs
Electrolyte	Electrolyte	55	55	Fluid and electrolyte disorders
Endocrine	Endocrine	48,51,52,53,58	48,51,52,53,58	Disorders of lipid metabolism,Nutritional deficiencies,Other endocrine disorders,Other nutritional; endocrine; and metabolic disorders,Thyroid disorders
Genitourinary	Urogenital	160,161,162,163, 164,165,166	160,162,163,164,16 5,166,168	Calculus of urinary tract,Genitourinary symptoms and ill-defined conditions,Hyperplasia of prostate,Inflammatory conditions of male genital organs,Inflammatory diseases of female pelvic organs,Other diseases of bladder and urethra,Other diseases of kidney and ureters,Other male genital disorders
Hematology	Hematology	59,60,61,62,63,64	59,60,61,62,63,64	Acute posthemorrhagic anemia,Coagulation and hemorrhagic disorders,Deficiency and other anemia,Diseases of white blood cells,Other hematologic conditions,Sickle cell anemia
Infection	Infection	1,10,122,124,125, 126,135,142,148, 159,2,201,248,3,4 ,5,9,90,92	1,10,122,124,125,1 26,142,148,159,197 ,2,201,246,247,248, 3,4,5,9,90,92	Acute and chronic tonsillitis,Acute bronchitis,Appendicitis and other appendiceal conditions,Bacterial infection; unspecified site,Fever of unknown origin,Gangrene,HIV infection,Immunizations and screening for infectious disease,Infective arthritis and osteomyelitis (except that caused by tuberculosis or sexually transmitted di,Inflammation; infection of eye (except

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				that caused by tuberculosis or sexually transmitteddisease),Intestinal infection,Lymphadenitis,Mycoses,Other upper respiratory infections,Otitis media and related conditions,Peritonitis and intestinal abscess,Pneumonia (except that caused by tuberculosis or sexually transmitted disease),Septicemia (except in labor),Sexually transmitted infections (not HIV or hepatitis),Skin and subcutaneous tissue infections,Tuberculosis,Urinary tract infections
	Influenza	123	123	Influenza
Musculoskeletal and integumentary	Musculosketal	197,198,199,200, 203,204,205,206, 207	173,198,199,200,20 3,204,205,206,207	Chronic ulcer of skin,Osteoarthritis,Osteoporosis,Other diagnostic procedures on skin subcutaneous tissue fascia and breast,Other inflammatory condition of skin,Other non-traumatic joint disorders,Other skin disorders,Pathological fracture,Skin and subcutaneous tissue infections,Spondylosis; intervertebral disc disorders; other back problems
	Connective	144,202,210,211, 253,54,57,86,87,8 8,89,91,94	144,202,210,211,25 3,54,57,86,87,88,89 ,91,94	Allergic reactions,Blindness and vision defects,Cataract,Glaucoma,Gout and other crystal arthropathies,Immunity disorders,Other connective tissue disease,Other ear and sense organ disorders,Other eye disorders,Regional enteritis and ulcerative colitis,Retinal detachments; defects; vascular occlusion; and retinopathy,Rheumatoid arthritis and related disease,Systemic lupus erythematosus and connective tissue

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				disorders
Neoplasm	Malignancy	12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,36,37,38,39,40,41,42,43,44,45,47	12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,36,37,38,39,40,41,42,43,44,45,47	Cancer of bladder,Cancer of bone and connective tissue,Cancer of breast,Cancer of bronchus; lung,Cancer of cervix,Cancer of colon,Cancer of esophagus,Cancer of kidney and renal pelvis,Cancer of liver and intrahepatic bile duct,Cancer of other female genital organs,Cancer of other GI organs; peritoneum,Cancer of other male genital organs,Cancer of other urinary organs,Cancer of ovary,Cancer of pancreas,Cancer of prostate,Cancer of rectum and anus,Cancer of stomach,Cancer of testis,Cancer of thyroid,Cancer of uterus,Cancer; other and unspecified primary,Cancer; other respiratory and intrathoracic, Hodgkin's disease,Leukemias,Maintenance chemotherapy; radiotherapy,Malignant neoplasm without specification of site,Melanomas of skin,Multiple myeloma,Neoplasms of unspecified nature or uncertain behavior, Non-Hodgkin's lymphoma,Other and unspecified benign neoplasm,Other non-epithelial cancer of skin,Secondary malignancies

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Women's health and perinatal care	Women's health and perinatal care	167,168,169,170, 171,172,173,174, 175,176,177,178, 179,180,181,182, 183,184,185,187, 188,189,190,191, 192,193,194,195, 196,218,220,221, 223,224,46	167,169,170,171,172,173,174,175,176, 177,178,179,180,181,182,184,185,187, 188,189,190,191,192,193,194,195,196, 218,219,220,221,223,224,46	Benign neoplasm of uterus,Birth trauma,Contraceptive and procreative management,Early or threatened labor,Ectopic pregnancy,Endometriosis,Female infertility,Fetal distress and abnormal forces of labor,Fetopelvic disproportion; obstruction,Forceps delivery,Hemorrhage during pregnancy; abruptio placenta; placenta previa,Hypertension complicating pregnancy; childbirth and the puerperium,Induced abortion,Inflammatory diseases of female pelvic organs,Intrauterine hypoxia and birth asphyxia,Liveborn,Malposition; malpresentation,Menopausal disorders,Menstrual disorders,Nonmalignant breast conditions,OB-related trauma to perineum and vulva,Other complications of birth; puerperium affecting management of mother,Other complications of pregnancy,Other female genital disorders,Other perinatal conditions,Other pregnancy and delivery including normal,Ovarian cyst,Polyhydramnios and other problems of amniotic cavity,Postabortion complications,Previous C-section,Prolapse of female genital organs,Prolonged pregnancy,Respiratory distress syndrome,Short gestation; low birth weight; and fetal growth retardation,Spontaneous abortion,Umbilical cord complication
Renal	Renal	156,157,158	156,157,158,161	Acute and unspecified renal

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				failure,Chronic kidney disease,Nephritis; nephrosis; renal sclerosis,Other diseases of kidney and ureters
Respiratory	Respiratory and hypoxia	103,127,128,129, 130,131,132,133, 134,56	103,127,128,129,13 0,131,132,133,134, 135,56	Aspiration pneumonitis; food/vomitus,Asthma,Chronic obstructive pulmonary disease and bronchiectasis,Cystic fibrosis,Intestinal infection,Lung disease due to external agents,Other lower respiratory disease,Other upper respiratory disease,Pleurisy; pneumothorax; pulmonary collapse,Pulmonary heart disease,Respiratory failure; insufficiency; arrest (adult)
Functional group				
Psychiatry	Psychiatry	650,651,652,656, 657,658,659,663, 670	650,651,652,656,65 7,658,659,670	Adjustment disorders,Anxiety disorders,Attention-deficit conduct and disruptive behavior disorders,Attention-deficit, conduct, and disruptive behavior disorders,Impulse control disorders NEC,Impulse control disorders, NEC,Miscellaneous mental health disorders,Mood disorders,Personality disorders,Schizophrenia and other psychotic disorders,Screening and history of mental health and substance abuse codes
Symptomatic and care	Symptomatic and care	246,252,254,255, 256,000,000,000	252,254,255,256,25 7,258,259	Administrative/social admission,Fever of unknown origin,Malaise and fatigue,Medical examination/evaluation,Other aftercare,Other screening for suspected conditions (not mental disorders or infectious disease),Rehabilitation care;

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				fitting of prostheses; and adjustment of devices,Residual codes; unclassified
Syncope	Syncope	245,93	245,93	Conditions associated with dizziness or vertigo,Syncope
Others	Iatrogenic	0,237,238,2616	237,238,2616	Adverse effects of medical care,Complication of device; implant or graft,Complications of surgical procedures or medical care,E Codes: Adverse effects of medical care,Invalid procedure
	Congenital	208,209,212,213,214,215,216,217,219,654,655	208,209,212,213,214,215,216,217,654,655	Acquired foot deformities,Cardiac and circulatory congenital anomalies,Developmental disorders,Digestive congenital anomalies,Disorders usually diagnosed in infancy childhood or adolescence,Disorders usually diagnosed in infancy, childhood, or adolescence,Genitourinary congenital anomalies,Nervous system congenital anomalies,Other acquired deformities,Other bone disease and musculoskeletal deformities,Other congenital anomalies,Short gestation; low birth weight; and fetal growth retardation
	Environment	2611	2611	E Codes: Natural/environment,External cause codes: Natural/environment

Supplementary Table 2 Characteristics of acute coma cohort

	Total acute coma n (%)		Reversible coma n (%)		Hospitalization n (%)		30-day mortality n (%)		*p*-value
Total	205,747	(100·00)	93,598	(45·49)	85,712	(41·66)	26,437	(12·85)	<0·001
Sex									
Male	111,897	(54·39)	49,738	(53·14)	46,910	(54·73)	15,249	(57·68)	<0·001
Female	93,850	(45·61)	43,860	(46·86)	38,802	(45·27)	11,188	(42·32)	
Age	58·27	±23·04	39·81	±19·99	52·93	±22·93	70·99	±16·90	<0·001
Age group									
<18	61,756	(30·02)	38,509	(13·56)	19,661	(22·94)	3,586	(13·56)	<0·001
18-64	49,039	(23·83)	22,955	(23·88)	19,771	(23·07)	6,313	(23·88)	
≧65	94,952	(46·15)	32,134	(62·56)	46,280	(53·99)	16,538	(62·56)	
CCI index									
CCI≦1	133,867	(65·06)	73,552	(78·58)	46,694	(54·48)	13,621	(51·52)	<0·001
CCI>1	71,880	(34·94)	20,046	(21·42)	39,018	(45·52)	12,816	(48·48)	
Income									
Low	58,488	(28·43)	26,255	(28·05)	25,054	(29·23)	7,179	(27·15)	<0·001
Middle	73,869	(35·90)	35,899	(38·35)	29,228	(34·10)	8,742	(33·07)	
High	73,390	(35·67)	31,444	(33·60)	31,430	(36·67)	10,516	(39·78)	
Occupation									
Dependents of the insured individuals	62,271	(30·27)	27,616	(29·50)	26,700	(31·15)	7,955	(30·09)	<0·001
Civil servants, teachers, military, veterans	2,915	(1·42)	1,429	(1·53)	1,151	(1·34)	335	(1·27)	
Nonmanual workers and professionals	20,121	(9·78)	11,891	(12·70)	6,401	(7·47)	1,829	(6·92)	
Manual workers	72,036	(35·01)	29,707	(31·74)	31,824	(37·13)	10,505	(39·73)	
Other	48,404	(23·53)	22,955	(24·53)	19,636	(22·91)	5,813	(21·99)	
Urbanization									
Urban	83,476	(40·57)	41,892	(44·76)	31,882	(37·20)	9,702	(36·70)	<0·001
Suburban	76,632	(37·25)	33,150	(35·42)	33,456	(39·03)	10,026	(37·92)	
Rural	45,639	(22·18)	18,556	(19·82)	20,374	(23·77)	6,709	(25·38)	
Causes of acute coma									<0·001
Neurological cause group	56,790	(27·60)	22,153	(23·67)	24,430	(28·50)	10,207	(38·61)	<0·001
CNS	30,065	(14·61)	8,183	(8·74)	14,639	(17·08)	7,243	(27·40)	
Encephalopathy	6,700	(3·26)	2,616	(2·79)	3,573	(4·17)	511	(1·93)	
Seizure	2,225	(1·08)	1,157	(1·24)	1,020	(1·19)	48	(0·18)	
Trauma	17,800	(8·65)	10,197	(10·89)	5,198	(6·06)	2,405	(9·10)	
Medical cause group	137,330	(66·75)	65,158	(69·61)	57,007	(66·51)	15,165	(57·36)	
Alcohol	2,533	(1·23)	2,255	(2·41)	257	(0·30)	21	(0·08)	
Cardiovascular	19,367	(9·41)	7,938	(8·48)	8,148	(9·51)	3,281	(12·41)	
Diabetes and insulin	11,155	(5·42)	4,178	(4·46)	5,529	(6·45)	1,448	(5·48)	
Digestive	19,904	(9·67)	9,364	(10·00)	7,968	(9·30)	2,572	(9·73)	
Drugs	5,036	(2·45)	2,002	(2·14)	1,941	(2·26)	1,093	(4·13)	
Electrolyte	456	(0·22)	249	(0·27)	152	(0·18)	55	(0·21)	
Endocrine	2,427	(1·18)	1,086	(1·16)	904	(1·05)	437	(1·65)	
Genitourinary	3,463	(1·68)	1,836	(1·96)	1,327	(1·55)	300	(1·13)	
Hematology	587	(0·29)	292	(0·31)	228	(0·27)	67	(0·25)	
Infection	31,063	(15·10)	14,714	(15·72)	14,005	(16·34)	2,344	(8·87)	
Musculoskeletal and integumentary	6,144	(2·99)	3,659	(3·91)	2,208	(2·58)	277	(1·05)	
Neoplasm	10,062	(4·89)	3,938	(4·21)	4,459	(5·20)	1,665	(6·30)	
Renal	3,564	(1·73)	1,149	(1·23)	1,884	(2·20)	531	(2·01)	
Respiratory	9,419	(4·58)	3,550	(3·79)	5,007	(5·84)	862	(3·26)	
Women's health and perinatal care	12,150	(5·91)	8,948	(9·56)	2,990	(3·49)	212	(0·80)	
Functional cause group	11,627	(5·65)	6,287	(6·72)	4,275	(4·99)	1,065	(4·03)	
Psychiatry	4,765	(2·32)	2,923	(3·12)	1,827	(2·13)	15	(0·06)	
Symptoms	1,379	(0·67)	881	(0·94)	342	(0·40)	156	(0·59)	
Syncope	521	(0·25)	352	(0·38)	169	(0·20)	0	(0·00)	
Others	4,962	(2·41)	2,131	(2·28)	1,937	(2·26)	894	(3·38)	
Outcome									
ICU	54,614	(26·54)	0	(0·00)	39,144	(45·67)	15,470	(58·52)	<0·001
LSTs	84,538	(41·09)	10,578	(11·30)	50,056	(58·40)	23,904	(90·42)	<0·001
Rehab	29,273	(14·23)	4,816	(5·15)	23,728	(27·68)	729	(2·76)	<0·001
Nursing home	3,861	(1·88)	492	(0·53)	3,261	(3·80)	108	(0·41)	<0·001
Disable	13,514	(6·57)	2,856	(3·05)	10,629	(12·40)	29	(0·11)	<0·001

CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department;

ICU: intensive care units; LST: life-sustaining treatment;

Chi-Square Test analyzed category variables distribution among groups; continue variable by One-way ANOVA·

Supplementary Table 3 Generalized linear model analysis of acute coma patients

		Reversible coma v.s. 30-day mortality				Hospitalization v.s. 30-day mortality			
		OR (95%CI)	*p*-value	aOR (95%CI)	*p*-value	OR (95%CI)	*p*-value	aOR (95%CI)	*p*-value
Sex	Male vs Female	1·20 (1·17-1·23)	<0·0001	1·29 (1·25-1·33)	<0·0001	1·13 (1·10-1·16)	<0·0001	1·14 (1·10-1·17)	<0·0001
Age	19-64 vs ≤ 18 years old	0·34 (0·32-0·35)	<0·0001	0·44 (0·42-0·46)	<0·0001	0·57 (0·55-0·60)	<0·0001	0·59 (0·56-0·62)	<0·0001
	≥ 65 vs ≤ 18 years old	0·18 (0·17-0·19)	<0·0001	0·26 (0·25-0·27)	<0·0001	0·52 (0·49-0·53)	<0·0001	0·44 (0·42-0·46)	<0·0001
CCI	> 1 vs ≤ 1	0·29 (0·28-0·30)	<0·0001	0·44 (0·42-0·45)	<0·0001	0·88 (0·87-0·91)	<0·0001	1·04 (1·01-1·07)	0·0219
Income	Middle vs low group	1·22 (1·18-1·26)	<0·0001	1·58 (1·52-1·64)	<0·0001	1·17 (1·13-1·21)	<0·0001	1·30 (1·25-1·35)	<0·0001
	High vs low group	1·37 (1·33-1·42)	<0·0001	1·33 (1·28-1·37)	<0·0001	1·12 (1·08-1·16)	<0·0001	1·12 (1·09-1·17)	<0·0001
Occupation	Dependents of the insured individuals vs others	0·82 (0·72-0·92)	0·0012	0·83 (0·73-0·95)	0·0055	0·99 (0·87-1·11)	0·7416	0·94 (0·83-1·07)	0·3469
	Civil servants, teachers, military, veterans vs others	1·53 (1·34-1·74)	<0·0001	0·93 (0·81-1·07)	0·3002	1·02 (0·89-1·16)	0·774	0·84 (0·74-0·97)	0·0136
	Nonmanual workers and professionals vs others	0·67 (0·59-0·75)	<0·0001	0·84 (0·74-0·96)	0·0084	0·88 (0·78-1·00)	0·0503	0·89 (0·78-1·01)	0·0799
	Manual workers vs others	0·93 (0·82-1·05)	0·2501	1·04 (0·91-1·18)	0·6073	0·99 (0·87-1·12)	0·8258	1·01 (0·89-1·15)	0·8776
Urbanization	Urban	0·77 (0·74-0·79)	<0·0001	0·83 (0·80-0·86)	<0·0001	1·01 (0·98-1·05)	0·3561	1·05 (1·01-1·08)	0·0064
	Urbanization	0·64 (0·62-0·66)	<0·0001	0·77 (0·74-0·80)	<0·0001	0·93 (0·89-0·96)	<0·0001	0·98 (0·94-1·02)	0·2124
Causes of coma	**Neurological group**	0·37 (0·34-0·39)	<0·0001	0·55 (0·51-0·59)	<0·0001	0·60 (0·56-0·64)	<0·0001	0·70 (0·65-0·75)	<0·0001
	CNS	0·47 (0·44-0·52)	<0·0001	0·68 (0·62-0·74)	<0·0001	0·99 (0·96-1·02)	0·1051	1·09 (1·00-1·19)	0·0517
	Encephalopathy	2·15 (1·90-2·43)	<0·0001	4·08 (3·59-4·63)	<0·0001	2·21 (1·86-3·65)	<0·0001	4·24 (3·75-4·80)	<0·0001
	Seizure	10·11 (7·50-13·64)	<0·0001	8·32 (6·15-11·24)	<0·0001	9·47 (7·07-13·24)	<0·0001	9·01 (6·67-12·17)	<0·0001
	Trauma	1·78 (1·63-1·95)	<0·0001	1·75 (1·59-1·92)	<0·0001	1·00 (0·91-1·10)	0·9585	1·02 (0·92-1·11)	0·7595
	Medical group	0·73 (0·68-0·78)	<0·0001	1·39 (1·30-1·49)	<0·0001	0·94 (0·87-1·00)	0·0641	1·16 (1·09-1·25)	<0·0001
	Alcohol	45·05 (29·11-69·72)	<0·0001	33·8 (21·81-52·38)	<0·0001	5·65 (3·60-8·88)	<0·0001	5·20 (3·31-8·17)	<0·0001
	Cardiovascular	1·02 (0·93-1·11)	0·7406	2·04 (1·86-2·24)	<0·0001	1·15 (1·05-1·25)	0·0027	1·50 (1·37-1·65)	<0·0001
	Diabetes and insulin	1·21 (1·10-1·34)	0·0001	3·13 (2·82-3·47)	<0·0001	1·76 (1·60-1·94)	<0·0001	2·31 (2·09-2·55)	<0·0001
	Digestive	1·53 (1·40-1·67)	<0·0001	2·53 (2·31-2·78)	<0·0001	1·43 (1·31-1·57)	<0·0001	1·69 (1·54-1·85)	<0·0001
	Drugs	0·77 (0·69-0·86)	<0·0001	0·72 (0·65-0·81)	<0·0001	0·82 (0·74-0·91)	0·0003	0·82 (0·73-0·91)	0·0003
	Electrolyte	1·90 (1·40-2·57)	<0·0001	2·96 (2·17-4·04)	<0·0001	1·28 (0·93-1·75)	0·1342	1·53 (1·11-2·11)	0·0091
	Endocrine	1·04 (0·91-1·19)	0·5473	1·49 (1·29-1·72)	<0·0001	0·96 (0·83-1·10)	0·5139	1·15 (1·00-1·32)	0·0521
	Genitourinary	2·57 (2·22-2·97)	<0·0001	4·41 (3·80-5·12)	<0·0001	2·04 (1·76-2·37)	<0·0001	2·59 (2·23-3·01)	<0·0001
	Hematology	1·83 (1·39-2·41)	<0·0001	2·53 (1·90-3·36)	<0·0001	1·57 (1·18-2·09)	0·0018	1·83 (1·38-2·44)	<0·0001
	Infection	2·63 (2·41-2·88)	<0·0001	4·26 (3·88-4·67)	<0·0001	2·76 (2·52-3·02)	<0·0001	3·36 (3·07-3·69)	<0·0001
	Musculoskeletal and integumentary	5·54 (4·79-6·41)	<0·0001	8·16 (7·04-9·47)	<0·0001	3·68 (3·17-4·27)	<0·0001	4·35 (3·75-5·05)	<0·0001
	Neoplasm	0·99 (0·90-1·09)	0·8747	2·06 (1·86-2·28)	<0·0001	1·24 (1·12-1·36)	<0·0001	1·57 (1·42-1·73)	<0·0001
	Renal	0·91 (0·80-1·03)	0·142	2·30 (2·01-2·62)	<0·0001	1·64 (1·45-1·86)	<0·0001	2·21 (1·95-2·51)	<0·0001
	Respiratory	1·73 (1·55-1·93)	<0·0001	3·54 (3·16-3·96)	<0·0001	2·68 (2·41-2·98)	<0·0001	3·57 (3·20-3·98)	<0·0001
	Women's health and perinatal care	17·71 (15·13-20·72)	<0·0001	11·86 (10·11-13·92)	<0·0001	6·51 (5·55-7·64)	<0·0001	5·44 (4·63-6·40)	<0·0001
	Functional group	(ref· of coma group)							
	Psychiatry	81·68 (48·90-136·46)	<0·0001	57·02 (34·11-95·33)	<0·0001	56·13 (33·69-93·92)	<0·0001	48·29 (28·88-80·77)	<0·0001
	Symptoms	2·37 (1·97-2·86)	<0·0001	2·78 (2·30-3·38)	<0·0001	1·01 (0·82-1·24)	0·9106	1·11 (0·90-1·37)	0·3158
	Syncope	NC		NC		NC		NC	
	Others	(ref of causes of coma)							

aOR: adjusted odds ratio; CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department; ICU: intensive care units; LST: life-sustaining treatment;

Syncope: no convergence

Supplementary Table 4 Characteristics of acute coma hospitalization within 14 days

	Total acute coma		Acute coma						
			Reversible coma		Hospitalization		30-day mortality		
	n	(%)	n	(%)	n	(%)	n	(%)	*p*-value
Total	231,516	(100·00)	65,711	(28·38)	50,636	(21·87)	11,5169	(49·75)	<0·001
Sex									
Male	125,340	(54·14)	34,157	(51·98)	27,705	(54·71)	63,478	(55·12)	<0·001
Female	106,176	(45·86)	31,554	(48·02)	22,931	(45·29)	51,691	(44·88)	
Age	60·08	±22·53	46·51	±21·33	52·26	±22·72	71·27	±16·65	<0·001
Age group									
<18	61,620	(26·62)	32,542	(49·52)	18,623	(36·78)	10,455	(9·08)	<0·001
18-64	54,757	(23·65)	18,393	(27·99)	14,918	(29·46)	21,446	(18·62)	
≧65	115,139	(49·73)	14,776	(22·49)	17,095	(33·76)	83,268	(72·30)	
CCI index									
CCI≦1	142,468	(61·54)	55,558	(84·55)	34,629	(68·39)	52,281	(45·40)	<0·001
CCI>1	89,048	(38·46)	10,153	(15·45)	16,007	(31·61)	62,888	(54·60)	
Income									
Low	77,350	(33·41)	17,393	(26·47)	13,002	(25·68)	46,955	(40·77)	<0·001
Middle	82,140	(35·48)	23,532	(35·81)	19,238	(37·99)	39,370	(34·19)	
High	72,026	(31·11)	24,786	(37·72)	18,396	(36·33)	28,844	(25·04)	
Occupation									
Dependents of the insured individuals	72,965	(31·52)	19,801	(30·13)	16,415	(32·42)	36,749	(31·91)	<0·001
Civil servants, teachers, military personnel, veterans	2,974	(1·28)	994	(1·51)	703	(1·39)	1,277	(1·11)	
Nonmanual workers and professionals	20,109	(8·69)	10,048	(15·29)	5,478	(10·82)	4,583	(3·98)	
Manual workers	82,064	(35·45)	19,267	(29·32)	16,492	(32·57)	46,305	(40·21)	
Other	53,404	(23·07)	15,601	(23·74)	11,548	(22·81)	26,255	(22·80)	
Urbanization									
Urban	156,602	(67·64)	48,471	(73·76)	34,912	(68·95)	73,219	(63·58)	<0·001
Suburban	71,024	(30·68)	16,143	(24·57)	14,815	(29·26)	40,066	(34·79)	
Rural	3,890	(1·68)	1,097	(1·67)	909	(1·80)	1,884	(1·64)	
Causes of coma									<0·001
Neurological group	75,399	(32·57)	20,542	(27·24)	26,165	(34·71)	28,692	(38·05)	<0·001
CNS	41,353	(54·85)	5,237	(25·49)	18,248	(69·74)	17,868	(62·28)	
Encephalopathy	9,753	(12·94)	2,015	(9·81)	1,728	(6·60)	6,010	(20·95)	
Seizure	4,053	(5·38)	2,184	(10·63)	1,466	(5·60)	403	(1·40)	
Trauma	20,240	(26·84)	11,106	(54·06)	4,723	(18·05)	4,411	(15·37)	
Medical group	141,892	(61·29)	36,644	(25·83)	21,244	(14·97)	84,004	(59·20)	
Alcohol	7,260	(5·12)	6,650	(18·15)	389	(1·83)	221	(0·26)	
Cardiovascular	20,753	(14·63)	3,152	(8·60)	1,686	(7·94)	15,915	(18·95)	
Digestive	17,023	(12·00)	3,111	(8·49)	1,896	(8·92)	12,016	(14·30)	
DM & Insulin	17,795	(12·54)	4,933	(13·46)	2,425	(11·41)	10,437	(12·42)	
Drugs	8,362	(5·89)	2,594	(7·08)	2,149	(10·12)	3,619	(4·31)	
Electrolyte	813	(0·57)	421	(1·15)	104	(0·49)	288	(0·34)	
Endocrine	3,439	(2·42)	1,362	(3·72)	762	(3·59)	1,315	(1·57)	
Genitourinary	1,302	(0·92)	178	(0·49)	116	(0·55)	1,008	(1·20)	
Hematology	678	(0·48)	256	(0·70)	124	(0·58)	298	(0·35)	
Infection	24,906	(17·55)	2,723	(7·43)	5,558	(26·16)	16,625	(19·79)	
Musculoskeletal and integumentary	2,301	(1·62)	588	(1·60)	507	(2·39)	1,206	(1·44)	
Neoplasm	9,804	(6·91)	222	(0·61)	249	(1·17)	9,333	(11·11)	
Renal	4,108	(2·90)	131	(0·36)	342	(1·61)	3,635	(4·33)	
Respiratory	10,968	(7·73)	1,421	(3·88)	2,019	(9·50)	7,528	(8·96)	
Women's health and perinatal care	12,380	(8·72)	8,902	(24·29)	2,918	(13·74)	560	(0·67)	
Functional group	14,225	(6·14)	8,525	(59·93)	3,227	(22·69)	2,473	(17·38)	
Psychiatry	5,665	(39·82)	3,008	(35·28)	2,545	(78·87)	112	(4·53)	
Symptoms	5,775	(40·60)	4,766	(55·91)	257	(7·96)	752	(30·41)	
Syncope	785	(5·52)	612	(7·18)	173	(5·36)	0	(0·00)	
Others	2,000	(14·06)	139	(1·63)	252	(7·81)	1,609	(65·06)	
Outcome									
ICU	56,648	(28·28)	327	(0·58)	40,207	(70·97)	16,114	(28·45)	<0·001
LST	161,924	(69·94)	59,493	(36·74)	22,722	(14·03)	79,709	(49·23)	<0·001
Rehab	108,716	(46·96)	56,008	(51·52)	12,798	(11·77)	39,910	(36·71)	<0·001
Disable	13,797	(5·96)	1,379	(9·99)	4,972	(36·04)	7,446	(53·97)	<0·001
Nursing case	5,145	(2·22)	139	(2·70)	941	(18·29)	4,065	(79·01)	<0·001

CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department; ICU: intensive care units; LST: life-sustaining treatment;

Chi-Square Test analyzed category variables distribution among groups; continue variable by One-way ANOVA·

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Incidence, Causes, and Prognostic Outcomes of Acute Coma: A Nationwide Population-Based Retrospective Cohort Study in Taiwan

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ORIGINAL WORK

Incidence, Causes, and Prognostic Outcomes of Acute Coma: A Nationwide Population-Based Retrospective Cohort Study in Taiwan

ABSTRACT

Objectives: Identifying the underlying cause of acute coma is crucial for improving outcomes in this time-sensitive medical emergency. This study aimed to explore the clinical characteristics, incidence, causes, and outcomes of acute coma.

Design: A nationwide population-based retrospective cohort study..

Participants: Among 99,217,322 ED visits between 2000 and 2017, 419,480 acute coma events were identified. After excluding visits with only acute coma diagnosis codes lacking detailed information, individuals without sociodemographic data, or those with prior nursing home residence or disability, a total of 205,747 first-ever acute coma cases constituted the final research cohort.

Primary and secondary outcome measures: The primary outcomes included the acute coma event rate, incidence rates stratified by age, and underlying causes categorized into 23 clinical groups by AHRQ Clinical Classification Software (CCS). Secondary outcomes assessed were reversible coma,

hospitalization rates, 30-day mortality, one-year medical utilization, and long-term functional outcomes. Cox regression models identified factors influencing long-term mortality.

Results: The overall event rate for acute coma was 4.23 per 1,000 ED visits, and the incidence rate was 0.93 per 1,000 person-years. The median age of cases was 58.27 years (SD 23.04), with a male predominance (58.90%). Infection and central nervous system (CNS)-related causes were most prevalent. Of these cases, 45.49% experienced reversible coma, 41.66% required hospitalization, and the 30-day mortality group accounted for 12.85%. CNS and drug-related causes contributed to increased 30-day mortality, while psychiatric, alcohol, women's health and perinatal care, and seizure are causes linked to reversible coma. Patients frequently required intensive care (26.54%), life-sustaining treatments (41.09%), or experienced disability (6.57%) within one year. Generalized estimating equations revealed significantly lower odds of reversible coma for CNS (aOR, 0.68; 95% CI, 0.62 to 0.74; $p < .0001$) and drug-related causes (aOR, 0.72; 95% CI, 0.65 to 0.81; $p < .0001$), indicating higher mortality risk. Cox regression analysis showed elevated long-term mortality risks associated with drug-related causes (aHR, 1.30; 95% CI, 1.20 to 1.41; $p < .001$), neoplasms (aHR, 1.18; 95% CI, 1.11 to 1.25; $p < .001$), and

symptoms-related causes (aHR, 1.44; 95% CI, 1.24 to 1.67; p < .001).

Conclusion: Infection and CNS disorders were identified as the most common etiologies of acute coma, with CNS and drug-related causes significantly associated with increased short-term and long-term mortality. This study demonstrates the efficacy of using CCS groups for aggregating ICD codes in acute coma research, providing critical insights for enhancing clinical management and outcomes.

Keywords

Coma, Clinical Classifications Software, Incidence, Risk factors, Natural history studies, Prognosis

Search Terms

Clinical Neurology: Coma,

Epidemiology: Incidence studies,

Epidemiology: Risk factors in epidemiology,

Epidemiology: Natural history studies (prognosis),

Clinical Neurology: Prognosis

Coma, Clinical Classifications Software, Incidence, Risk factors, Natural history studies, Prognosis

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We utilized the AHRQ Clinical Classification Software (CCS) to develop a clinical research model for investigating acute coma and its clinical characteristics.

⇒ This is the first nationwide retrospective cohort study to utilize longitudinal data, offering insights into the clinical progression and mortality risk of first-ever acute coma.

⇒ The proposed research model enables international comparative studies of acute coma, advancing evidence-based practice and supporting the development of AI algorithms for coma management.

⇒ The absence of coma scale data to accurately define the first-ever acute coma cohort represents a limitation, potentially affecting the precision of acute coma incidence estimation.

⇒ Heterogeneity in the results may arise from variability in the classification of underlying mechanisms and causes of acute coma across differing definitions, datasets, and settings.

INTRODUCTION

Acute coma is a critical time-sensitive condition with heterogeneous causes that requires urgent attention and has significant impacts on patients and healthcare professionals.[1] It is characterized by profound failure of the neurological system responsible for maintaining arousal and awareness, leading to either a reflex response or no response to external stimuli at all.[2] Prior studies estimate that 1-5% of patients presenting to the emergency department (ED) have a disturbance in consciousness.[3 4] Emergency care researchers often categorize acute coma into three etiological factors: primary CNS disease, severe medical conditions that affect the CNS secondarily, or functional such as psychogenic disorder.[5 6] The clinical course of acute coma has been classified into three main categories: reversible coma, where patients recover quickly after ED management and can be discharged without any functional deficits; mortality group consisting of patients who do not survive their coma event despite medical interventions; and hospitalization group, which includes patients requiring hospitalization that may need intensive care or life-sustaining treatments (LSTs), or complicated with long-term disabilities.[7 8] Major challenge in studying acute coma is its heterogeneous nature, with multiple possible contributing factors often present in a single patient. Variations in acute coma

study results may arise due to differences in definitions, cause classifications, and follow-up periods.[9] These factors can affect outcomes and complicate direct comparisons between studies, underscoring the need for standardized methodologies.[10] Despite the urgent need for a better understanding clinical nature of acute coma, there is a lack of large-scale longitudinal studies that can comprehensively address the incidence, causes, clinical course, and outcomes of acute coma.

The Agency for Healthcare Research and Quality (AHRQ) has developed the Clinical Classification Software (CCS) to provide a standardized method for classifying diagnosis codes into CCS categories based on clinical characteristics.[11 12] The CCS categories employ the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Clinical Modification (ICD-10-CM) classification systems to aggregate large numbers of ICD diagnostic codes into 285 clinically meaningful categories, thereby making clinical research more feasible. Our study aims to (1) estimate acute coma incidence, (2) use the CCS to identify acute coma causes, and (3) investigate the clinical course and outcomes.

MATERIALS AND METHODS

Study design and setting

In this nationwide population-based retrospective cohort study, we utilized

Taiwan National Health Insurance Research Database (NHIRD) to examine ED visits between January 1, 2000, and December 31, 2017. The NHIRD, managed by the Ministry of Health and Welfare, offered a comprehensive dataset with information on demographics, comorbidities, hospitalization, functional status, and mortality. This study was conducted with the approval of the local ethics board and involved no direct patient interaction. We carried out a retrospective analysis of claims data, ensuring all personal identifiers were encrypted to uphold patient confidentiality.

Acute coma participants' definition

Given the nature of this study, we utilized the NHIRD dataset to investigate acute coma incidences. However, the NHIRD dataset lacks specific indicators, such as the Glasgow Coma Scale (GCS), to accurately represent coma status. Consequently, we relied on the judgment of emergency physicians in diagnosing acute coma instances, especially in cases where there was no explicit diagnosis but an indication of coma in the ED's diagnoses. We employed DynaMed (2020) Coma International Classification of Diseases (ICD) codes to define acute coma objectively.[13] These codes encompass a range of acute coma conditions, including "780.1" and "780.01" for comatose, "780.09" for other alterations of consciousness, "R40.0" for somnolence, "R40.1" for stupor, "R40.2" for unspecified coma, and "S06.7" for intracranial injury-related

coma. Therefore, our study population consisted of cases that included any of these codes within the three diagnoses upon ED discharge records and remained as the final research cohort (Figure 1). The present study implemented several exclusion criteria to ensure precise estimation of the cause, disease progression, and clinical outcomes associated with acute coma. First, we omitted cases lacking comprehensive sociodemographic data. Second, we excluded those who were undergoing life-sustaining treatments or were disabled or residing in a nursing home prior to the first-ever acute coma event. Additionally, cases diagnosed with acute coma in the ED that the CCS could not further classify due to the absence of additional diagnostic information from the ED or inpatient records were excluded from the study. To rule out hospitalizations potentially unrelated to the acute coma events, we excluded samples in which hospitalization occurred more than 14 days after the acute coma index date.

Incidence estimates

We estimated the annual acute coma event rate from 2000 to 2017, with acute coma events as the unit of analysis. The event rate of acute coma is calculated by dividing the number of events by ED visits. In addition, we determined crude age group-stratified incidence rates were determined per 1000 person-years, with denominators based on the number of insured individuals during the year,

taking into account their survival status and the person-years they contributed within that year. Considering insured individuals' survival status and person-years contributed and reported age-specific incidence rates in pediatric (1-18), adult (19-64), and senior adult (65+) groups with corresponding summary statistics.

Clinical course, causes, and outcomes assessment

The study explored the clinical course of acute coma using each patient's first-ever event as the unit of analysis. The index date was set as the date of the first diagnosis of acute coma. ED visits were categorized into reversible coma, hospitalization, and 30-day mortality.[14] Individuals who died within 30 days of the acute coma ED index date were classified as the 30-day mortality group. Those requiring hospitalization within seven days post-episode but not dying within 30 days constituted the hospitalization group. Patients diagnosed with acute coma in the ED without needing hospitalization or facing death were categorized as the reversible coma group.

Using CCS methodology,[12 15 16] we categorized ICD codes from death or hospitalization into 23 acute coma causes (Supplementary Table 1) and a statistical analysis plan is available in the (Supplementary Program). The diagnosis sequence begins with death, hospitalization, and ED diagnosis if no death or hospitalization occurs. These causes were further classified into three

etiological mechanisms: (1) primary CNS diseases (neurological etiology), (2) medical conditions affecting the CNS secondarily (medical etiology), and (3) functional etiology.[5] Neurological etiology included acute CNS insult, chronic neurodegenerative encephalopathy, paroxysmal seizure disorders, and brain trauma. Medical etiology included alcohol-related coma, drugs, and organ system dysfunction. Functional factors included psychogenic disorders, symptoms, syncope, and other related causes. Patients were followed for one year to evaluate short-term outcomes (30-day mortality or reversible course) and long-term outcomes (ICU admission, LSTs,[17] rehabilitation, disability status, or nursing home residency).

Statistical analysis

We used χ^2 tests to analyze baseline categorical characteristics and compared continuous variables' mean among coma groups with One-Way ANOVA. Generalized estimating equations (GEE) were used to estimate acute coma's adjusted odds ratio (aOR), accounting for multiple causes and covariates like sex, age, Charlson Comorbidity Index (CCI), occupation, urbanization, and income. Survival analysis was conducted for reversible and hospitalization groups, tracking survival probability and calculating time to event (death) or censoring. Cox regression investigated potential causes of death events, with hazard ratios identifying factors affecting long-term outcomes. Analyses were

performed with SAS software, version 9.4, and a significance level of $p < 0.05$.

RESULTS

Cohort characteristics and clinical course estimate

Among 99,217,322 ED visits between 2000 and 2017, 419,480 acute coma events were identified. Of these, 365,675 patients were discharged or hospitalized within seven days. After excluding 4,385 ED visits with only acute coma diagnosis code, lacking further information, and participants lacking sociodemographic data or with prior nursing home or disabled status, 205,747 cases remained in the final research cohort (Figure 1). The cohort clinical course classified 93,598 (45.49%) as reversible acute coma group, 85,712 (41.66%) as hospitalization group, and 26,437 (12.85%) as 30-day mortality group. The study population was 54.39% male, with an average age of 58.27 (SD 23.04) years (Supplementary Table 2).

Incidence of acute coma

Table 1 analyzes ICD diagnosis codes for acute coma events, revealing: (1) a crude event rate of 4.23 per 1,000 ED visits, (2) an average overall incidence rate of 0.93 per 1,000 person-years, and (3) age-specific incidence rates, 0.13 for pediatric, 0.57 for middle-aged, and 7.13 for senior adult groups. A significant mean decrease in incidence rate in 2016 suggests that age and temporal factors may influence acute coma incidence.

Causes and outcomes of acute coma

Supplementary Table 1 presents leading acute coma causes, including infection (15.10%), CNS (14.61%), digestive (9.67%), cardiovascular (9.41%), and trauma-related (8.65%). Common reversible causes included infection (15.72%), trauma (10.89%), digestive (10.00%), women's health and perinatal care (9.56%), and CNS (8.74%). Hospitalization for acute coma frequently resulted from CNS (17.08%), infection (16.34%), cardiovascular (9.51%), digestive (9.30%), and diabetes and insulin (6.45%). Leading causes of death were CNS (27.40%), cardiovascular (12.41%), digestive (9.73%), trauma (9.10%), and infection (8.87%). Medical etiologies were the primary factor (66.75%), with neurological (27.60%) and functional (5.65%) etiologies also contributing. Short-term outcomes indicated 45.49% of cases left the ED without sequelae, 12.85% experienced 30-day mortality, and 41.66% necessitated hospitalization within seven days. Elderly patients had a significantly higher mortality rate of 62.56% compared to 11.56% for younger patients. The one-year follow-up showed ICU treatment (26.54%), LSTs (41.09%), rehabilitation (14.23%), disability (6.57%), and nursing care (1.88%).

Multivariate analysis of acute coma

The GEE analysis identified covariates significantly associated with increased acute coma mortality, including females, older age, higher CCI

scores, low income, and rural residence (Supplementary Table 3). Compared to other causes, CNS (adjusted odds ratio [aOR], 0.68; 95% CI: 0.62 to 0.74; p < .0001) and drug-related causes (aOR, 0.72; 95% CI: 0.65 to 0.81; p < .0001) had lower odds of reversible coma compared to 30-day mortality, while psychiatric (aOR, 57.02; 95% CI: 34.11 to 95.33; p < .0001), alcohol (aOR, 33.8; 95% CI: 21.81 to 52.38; p < .0001), women's health and perinatal care (aOR, 11.86; 95% CI: 10.11 to 13.92; p < .0001), seizures (aOR, 8.32; 95% CI: 6.15 to 11.24; p < .0001), and musculoskeletal/integumentary causes (aOR, 8.16; 95% CI: 7.04 to 9.47; p < .0001) had higher odds. Drug causes had lower odds of hospitalization compared to mortality (aOR, 0.82; 95% CI: 0.73 to 0.91; p=.0003), while psychiatry (aOR, 48.29; 95% CI: 28.88 to 80.77; p < .0001), seizure (aOR, 9.01; 95% CI: 6.67 to 12.17; p < .0001), women's health and perinatal care (aOR, 5.44; 95% CI: 4.63 to 6.40; p < .0001), and alcohol (aOR, 5.20; 95% CI: 3.31 to 8.17; p < .0001) causes increased the odds. Compared to functional etiology, neurological etiology had lower odds of reversible coma (aOR, 0.55; 95% CI, 0.51 to 0.59, p < .0001) and hospitalization (aOR, 0.70; 95% CI 0.65 to 0.75, p < .0001), while medical etiology had higher odds of reversible coma (aOR, 1.39; 95% CI: 1.30 to 1.49, p < .0001) and hospitalization (aOR, 1.16; 95% CI: 1.09 to 1.25, p < .0001).

The Kaplan-Meier estimation (Supplementary Figure 1) and Cox proportional hazards regression (Table 2) revealed increased mortality risk associated with higher CCI score (adjusted hazard ratios [aHR], 1.08, 95% CI 1.07 to 1.09, p < .001), older age (aHR, 2.17, 95% CI 2.13 to 2.22, p < .001), manual labor (aHR, 1.03, 95% CI 1.02 to 1.04, p < .001), drug (aHR, 1.30, 95% CI 1.20 to 1.41, p < .001), neoplasm (aHR, 1.18, 95% CI 1.11 to 1.25, p < .001), and symptoms cause (aHR, 1.44, 95% CI 1.24 to 1.67, p < .001). In addition, the average mortality post-acute coma for the reversible group was observed at 7.10 years, while for the hospitalization group, it occurred at 6.41 years.

Sensitivity test of acute coma

To assess the robustness of our findings, we focused on the definition of an acute coma cohort, explicitly examining the first-ever episode that led to hospitalization within either a 7-day or 14-day period. Our analysis revealed no significant differences between these two cohort definitions in terms of clinical course subgroup distribution and cause classification for acute coma (see Supplementary Table 4). This suggests that our findings are consistent and reliable across different definitions.

DISCUSSION

Acute coma frequently represents a common pathway of organ dysfunction

from diverse causes, significantly impacting patients' survival and quality of life and straining healthcare resources. This study aims to explore the incidence density, causes, clinical courses, and outcomes of acute coma. Several methodological and result issues warrant discussion.

Methodology discussion

Our 18-year longitudinal retrospective cohort study employs the ICD coding system and the Clinical Classification Software (CCS) method to address the complexity of acute coma's causes and etiologies. This complexity, driven by a wide range of reversible and time-sensitive factors, poses significant challenges in synthesizing diverse clinical causes into a unified cohort for claims-based research. Previous studies have often relied on medical record reviews[18] or rigorously designed cohort studies,[19] lacking a comprehensive and longitudinal perspective. To bridge this research gap, we devised an innovative clinical research model integrating big data analytics with clinical investigation. This approach offers a novel framework for examining the multifaceted clinical scenarios related to acute coma through claims-based data, thereby opening new avenues for neuroscientific research and enhancing emergency medical decision-making systems.

Study design, population, and cohort definition

The Taiwan NHIRD, encompassing the entire population and offering

comprehensive medical services, facilitated a thorough analysis of acute coma's clinical nature. Besides, The large cohort of over 200,000 patients offered a robust population representation. Moreover, we defined the cohort based on one impaired consciousness in the ED study, where the average hospitalization duration was 6.4 days. Therefore, we included cases where the onset of acute coma and subsequent hospitalization occurred within seven days as part of the study cohort.[20] By excluding patients with prior nursing home residence or disability status it provides a better understanding of the true incidence and outcomes of first-ever acute coma.

Meanwhile, the lack of clinical coma scale data raises concerns about the accuracy of the methodology, which relies on ICD coding and the CCS method. Our study adopted a broader definition of acute coma, using ICD codes, covering various alterations of consciousness such as somnolence, stupor, unspecified coma, and intracranial injury-related coma. Our study adopted a broad range of acute coma diagnosis codes to capture various clinical scenarios.[21] We used ICD coding methodology covering the qualitative spectrum of 'decreased consciousness,' including somnolence, stupor, coma, and quantitative GCS score ranges [21]. We also included the current quantitative approach to coma assessment, coding GCS scores of 13-15 as R40.0

(somnolence), 9-12 as R40.1 (stupor), and ≤ 8 as R40.2 (coma, unspecified). This approach ensured a thorough representation of acute coma in our research sample.

Defined of acute coma causes

Integrating CCS with the ICD coding system in clinical research potentially offers a holistic and nuanced methodology for categorizing complex clinical data into clinically meaningful classes.[15] While established frameworks for transforming a myriad of ICD codes into clinically relevant categories that can guide clinical decision-making, inform policy interventions, or enable regular monitoring are not yet widespread,[12] In our study, we utilized CCS to condense 285 CCS categories into 23 clinically relevant causes of acute coma, rendering the study practically feasible and enabling the in-depth analysis of acute coma's multifaceted clinical manifestations. This approach facilitates large-scale, longitudinal, population-based studies in EDs, optimizing approaches to address acute coma's clinical nature.

Results discussion

Understanding the clinical characteristics of acute coma makes it crucial for intensivist clinicians to identify the cause to prevent disability[22] and emergency medical policy applications.

Causes, clinical courses, and outcomes

Infections, CNS disorders, digestive issues, cardiovascular events, and trauma

are leading causes of acute coma. Our research results are consistent with international findings, with infection being the most common cause.[23 24] Acute coma causes differ based on geography[25] or age.[23] For instance, poisoning contributes to approximately one-third of unconsciousness cases in Nordic countries.[25] In children, common causes are intoxication, epilepsy, infection, and traumatic brain injury.[18] CNS and infectious disorders are more common in adults and older adults.[18 21] The prominence of digestive causes for acute coma in our cohort may be due to the prevalence of hepatitis and hepatocellular carcinoma in Taiwan.[26] To facilitate a broader understanding of public health implications related to the potential etiologies and mechanisms underlying acute coma, and to enable meaningful comparisons with existing literature, we have classified the etiologies of acute coma into three major categories: neurological, medical, and functional factors.[5 6 27] This categorization approach aids in developing targeted intervention strategies and informs policy-making. Neurological causes account for about one-third of cases, while non-neurological causes comprise the remaining two-thirds.[28] Schmidt (2017) reported that neurological and medical etiologies each contributed to about 50% of acute coma cases.[5] Functional or psychogenic coma constituted around 5% of cases. It is worth further exploring the causes of coma

resulting from functional factors.

The clinical course of acute coma varies due to differing underlying causes or etiologies.[9 23] Over half of the first-ever acute coma patients required hospitalization or faced mortality. In contrast, the other nearly half demonstrated reversible outcomes. The short-term in-hospital mortality rate for patients with acute coma is about 5 -11%[3 20 29] with longer follow-up reaching 25%.[29] Our study found that 27.60% of acute coma cases were attributed to neurological etiology, and within the mortality group, 38.16% of cases had a neurological cause. This supports prior research indicating that clinical course is highly dependent on etiology.[23] Syncope and seizures are generally believed to be the most common causes of reversible coma. However, in our study, these two common causes accounted for only 1.33% of cases of overall acute coma. This may support researchers' definition of coma as a state of prolonged sustained unconsciousness lasting at least one hour.[30] Our emergency physicians may better understand syncope and seizure, improving diagnostic accuracy.[31] Study showed that twenty percent of patients with acute coma may have already been reversible on admission.[29] If these patients are monitored for two months after hospitalization, one-third of them may fully recover consciousness.[32] Our study found that approximately 45.49% of patients had reversible coma. The higher

proportion of reversible coma in our study may reflect a more lenient coding of coma or the higher quality of emergency medical care by emergency physicians in our study. These results suggest that the outcome of acute coma is highly dependent on the underlying cause and severity of the condition.[33] Regarding long-term outcomes, one-quarter of patients with first-ever acute coma necessitated ICU admission, and forty percent required LSTs within one year. The high percentage of patients in the LSTs group who require long-term care and have a high mortality rate, emphasizes the need for improved management strategies for patients with acute coma.[7]

Incidence

Our study found an acute coma event rate of 4.23 visits per 1,000 ED visits, consistent with the Schmidt et al. (2019) ED cohort study.[29] However, our results differ from those of another study that reported 0.29-0.40 cases of coma per 1,000 ED visits.[34] Based on the ICD code approach, studies suggested that acute coma is about 0.93-5% of all ED visits.[28 35]. Pediatric non-trauma coma studies also have reported incidences ranging from 0.3 to 1.6 per 1,000 person-years.[23] This disparity in results may be attributed to differences in research questions, study design, study population, or definitions.[36]

We investigated the incidence rates of acute coma in different age groups and temporal trends. The highest incidence rate of acute coma was observed

in the elderly age group, emphasizing the significance of this public health concern in the aging population. However, there is also some variability in the incidence rates over time. We found that the incidence rate stabilized at around 1 per 1,000 person-years from 2007 to 2015 and observed a significant mean decrease in the incidence rate in 2016 compared to previous years. Specifically, there was a significant mean decrease from 0.73 per 1,000 person-years in 2016 to 0.63 per 1,000 person-years in 2017. One possible explanation for reducing acute coma incidence during 2016-2017 is the transition from the ICD-9 to the ICD-10 coding system in 2015. We also found no significant difference in ED visits between 2014 and 2017 (5,904,262 vs 5,945,444, respectively). Thus, the substantial change in acute coma incidence could be an artifact of the ICD coding transition effect.[37]

Strengths and Limitations

This study has several strengths and limitations. Strengths include using nationwide longitudinal data to observe first-ever acute coma patterns, enabling tracking of clinical progression. The average post-acute coma mortality occurring seven years highlights its importance as a risk factor and common pathway for mortality. Additionally, the study employed AHRQ CCS methodology, facilitating regular monitoring of acute coma clinical information and enabling tailored intervention plans.

The present study has several limitations that need to be acknowledged. Firstly, the absence of a coma scale to accurately define the first-ever acute coma cohort represents a significant limitation. Instead, the study relied on acute coma-related diagnoses coded by emergency physicians in the ED, potentially leading to an underestimation of acute coma incidence and compromising the accuracy of identifying the causes of coma. Additionally, the conversion between ICD-9 and ICD-10 coding systems may introduce inaccuracies in estimating coma-related diagnoses due to potential discrepancies and inconsistencies in classification. Consequently, the reliability of the results may be affected. Furthermore, it is important to recognize that the acute coma diagnosis employed in this study may not fully capture the underlying causes or medical utilization, as multiple contributing pathologies could be involved due to potential multiple underlying pathologies.[29] The complexity of coma etiology and the potential presence of various underlying factors may limit the accuracy of attributing the diagnosis to a single cause. Moreover, a small proportion (about 2%) of acute coma patients presented in the ED lacked further diagnostic information, which reflects the challenge in diagnosing cases of coma with unknown origins and introduces potential uncertainty and incomplete data in the analysis. Another limitation is the

reliance on data limited to the year 2017, preventing examining the potential effects of the COVID-19 pandemic. Incorporating the impact of the pandemic would have enhanced the understanding of the significance of infections and central nervous system-related causes in estimating acute coma incidence. Finally, it should be noted that this study did not utilize the World Health Organization's (WHO) World Standard Population for age-specific rates adjustment, which may limit the generalizability and comparability of the findings with other studies that utilize standardized rates based on the WHO standard populations. These limitations should be considered when interpreting the study's results, and future research should address these limitations to enhance the robustness and applicability of the findings.

CONCLUSION

Acute coma often represents a common pathway of organ dysfunction with diverse causes or etiologies, significantly impacting mortality and disability. Our study demonstrates the innovative use of ICD codes aggregation to CCS groups in acute coma clinical study, providing valuable insights into its clinical nature. This research model has the potential to facilitate international comparative studies of acute coma characteristics using healthcare databases.

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Contributorship statement

Contributorship statement CY Lin took a lead role in conceptualizing the study and writing the original draft, and was responsible for formal data analysis. ML Chang verified the underlying data in the manuscript. MC Tsai contributed to study design, data curation, and formal data analysis and was responsible for data collection. JF Liang and ML Chang ensured accurate data analysis and interpretation and verified the manuscript's underlying data. CC Liu, YC Lee and ML Chang supervised the study, validated the results, and significantly contributed to reviewing and editing the manuscript. All authors participated in developing the study concept and design, analyzing and interpreting data, and preparing the manuscript. We have all approved the final manuscript and agree to be accountable for all aspects of the work, promising to appropriately

investigate and resolve any question related to the work's accuracy or integrity.

ML Chang acted as guarantor.

Patients or the public involvement

Patients or the public were not involved in our research's design, conduct, reporting, or dissemination plans.

Declarations

1) **Confirm the manuscript complies with all instructions to the authors**

   The authors confirm that our manuscript adheres to all the instructions provided for authors.

2) **Confirm that authorship requirements (see below) have been met and the final manuscript was approved by all authors**

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   The authors confirm that this work is original, unpublished elsewhere and respectfully request its consideration for acceptance in the esteemed journal.

4) **Confirm adherence to ethical guidelines and indicate ethical approvals (IRB) and use of informed consent, as appropriate (see below). Retrospective studies require a statement regarding IRB approval**

   All authors have completed the ICMJE conflict of interest form and declare

no conflicts of interest in relation to this manuscript. The study involved a retrospective analysis of encrypted unique personal identification data without direct patient involvement. Therefore, no patient consent was necessary for the completion of this study. As the corresponding author, I confirm that we complied with all applicable laws regarding data protection and privacy. No patients were involved. This study was a retrospective claim data analysis that included all encrypted unique personal identification. Ethics approval: IRB of Taipei City Hospital, number-TCHIRB-10807003-E.

5) Disclose Conflicts of Interest for all authors

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6) Confirm the use of reporting checklist (see below), if appropriate

The authors have confirmed the use of reporting checklists. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement when reporting observational studies and the Standards of Reporting of Neurological Disorders (STROND) for reporting incidence studies in neuroepidemiology.

Data Availability Statement

Taiwan National Health Insurance Research Database was provided by the National Health Insurance Administration and managed by the National Health Research Institutes.

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Table and Figure Titles

Figure 1 Flow diagram of the study
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Table 2 Multivariate Cox regression analysis of factors contributing to all-cause mortality in acute coma patients

Supplementary Figure 1 Survival analysis of acute coma patients
Supplementary Table 1 Clinical classification software for grouping the causes of acute coma
Supplementary Table 2 Characteristics of acute coma cohort
Supplementary Table 3 Generalized linear model analysis of acute coma patients
Supplementary Table 4 Characteristics of acute coma hospitalization within 14 days cohort
Supplementary statistical analysis plan SAS program using clinical classification

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Table 1 Acute coma event rate and incidence by year and age group

Year	ED visits	Coma events	Coma rate (‰)	Incidence (‰) (95% CI)	Age 1-18 Incidence (‰) (95% CI)	Age 19-64 Incidence (‰) (95% CI)	Age ≧ 65 Incidence (‰) (95% CI)
2000	4,519,482	10,330	2·29	0·45 (0·44-0·46)	0·08 (0·08-0·09)	0·30 (0·30-0·31)	7·74 (7·53-7·95)
2001	4,707,002	11,480	2·44	0·49 (0·48-0·50)	0·09 (0·08-0·10)	0·32 (0·32-0·33)	7·77 (7·57-7·97)
2002	5,028,446	12,567	2·50	0·53 (0·52-0·54)	0·10 (0·09-0·11)	0·34 (0·33-0·34)	7·78 (7·59-7·97)
2003	4,776,136	13,246	2·77	0·56 (0·55-0·57)	0·10 (0·09-0·10)	0·36 (0·35-0·36)	7·21 (7·04-7·38)
2004	5,354,185	16,072	3·00	0·67 (0·66-0·68)	0·11 (0·10-0·11)	0·44 (0·43-0·45)	7·58 (7·41-7·74)
2005	5,416,581	20,535	3·79	0·85 (0·83-0·86)	0·12 (0·11-0·13)	0·56 (0·54-0·57)	8·80 (8·63-8·97)
2006	5,171,689	21,769	4·21	0·89 (0·88-0·90)	0·13 (0·12-0·13)	0·57 (0·56-0·58)	8·59 (8·43-8·75)
2007	5,282,870	23,591	4·47	0·96 (0·94-0·97)	0·13 (0·12-0·14)	0·58 (0·57-0·60)	8·74 (8·59-8·89)
2008	5,191,529	25,548	4·92	1·02 (1·01-1·04)	0·14 (0·13-0·15)	0·63 (0·62-0·64)	8·53 (8·39-8·67)
2009	5,770,750	27,062	4·69	1·08 (1·07-1·09)	0·15 (0·14-0·16)	0·65 (0·64-0·67)	8·43 (8·30-8·57)
2010	5,878,033	31,184	5·31	1·23 (1·22-1·25)	0·17 (0·16-0·18)	0·73 (0·71-0·74)	9·27 (9·13-9·41)
2011	6,060,366	33,944	5·60	1·33 (1·32-1·35)	0·19 (0·18-0·20)	0·80 (0·78-0·81)	9·24 (9·11-9·37)
2012	6,098,194	34,259	5·62	1·33 (1·32-1·34)	0·19 (0·18-0·20)	0·79 (0·78-0·80)	8·60 (8·47-8·72)
2013	5,753,114	33,531	5·83	1·29 (1·28-1·31)	0·20 (0·19-0·21)	0·76 (0·75-0·77)	7·80 (7·69-7·91)
2014	5,904,262	34,917	5·91	1·34 (1·32-1·35)	0·19 (0·18-0·21)	0·78 (0·77-0·79)	7·48 (7·38-7·59)
2015	6,055,577	33,366	5·51	1·27 (1·25-1·28)	0·21 (0·19-0·22)	0·73 (0·72-0·74)	6·57 (6·47-6·66)
2016	6,303,662	19,355	3·07	0·73 (0·72-0·74)	0·09 (0·09-0·10)	0·39 (0·38-0·40)	3·70 (3·63-3·76)
2017	5,945,444	16,724	2·81	0·63 (0·62-0·64)	0·07 (0·07-0·08)	0·33 (0·32-0·34)	2·96 (2·90-3·02)
Total	99,217,322	419,480					
Average			4·23	0·93 (0·93-0·94)	0·13 (0·13-0·13)	0·57 (0·57-0·57)	7·13 (7·10-7·16)

CI: confidence interval; ED: emergency department;

Coma rate(‰)=acute coma events/1,000ED visits

Incidence of acute coma per 1,000 person-year

Table 2 Multivariate Cox regression analysis of factors contributing to all-cause mortality in acute coma patients

	Cox proportional hazards	
	aHR	*p*-value
Sex (male)	0·82 (0·80 - 0·84)	< 0·001
CCI (CCI>1)	1·08 (1·07 - 1·09)	< 0·001
Age (old age)	2·17 (2·13 – 2·22)	< 0·001
Income (high)	0·98 (0·97 - 1·00)	0·05
Occupation (manual)	1·03 (1·02 - 1·04)	< 0·001
Area (urban)	1·02 (1·01 - 1·04)	0·01
Neurological group		
CNS	0·83 (0·79 - 0·88)	< 0·001
Encephalopathy	0·93 (0·87 - 0·99)	0·04
Seizure	0·32 (0·26 - 0·39)	< 0·001
Trauma	0·48 (0·45 - 0·52)	< 0·001
Medical group		
Alcohol	0·39 (0·30 – 0·51)	< 0·001
Cardiovascular	0·94 (0·89 - 0·99)	0·02
Digestive	0·91 (0·86 - 0·96)	< 0·001
Drugs	1·30 (1·20 - 1·41)	< 0·001
Electrolyte	0·99 (0·78 - 1·25)	0·93
Endocrine	0·76 (0·67 - 0·86)	< 0·001
Genitourinary	0·43 (0·38 – 0·49)	< 0·001
Hematology	0·63 (0·49 - 0·80)	< 0·001
Infection	0·66 (0·63 - 0·69)	< 0·001
Musculoskeletal and integumentary	0·31 (0·28 - 0·35)	< 0·001
Neoplasm	1·18 (1·11 - 1·25)	< 0·001
Renal	1·05 (0·97 - 1·13)	0·21
Respiratory	0·80 (0·75 - 0·85)	< 0·001
Women's health and perinatal care	0·15 (0·13 - 0·18)	< 0·001
Functional group		
Psychiatry	0·05 (0·03 - 0·05)	< 0·001
Symptoms	1·44 (1·24 – 1·67)	< 0·001
Syncope	0·00	.
Others	0·47 (0·42 - 0·53)	< 0·001

Age (old age group), CCI (CCI>1 group), Income (high-income group), Area (urban), Occupation (manual), Sex (male)

Syncope: no convergence

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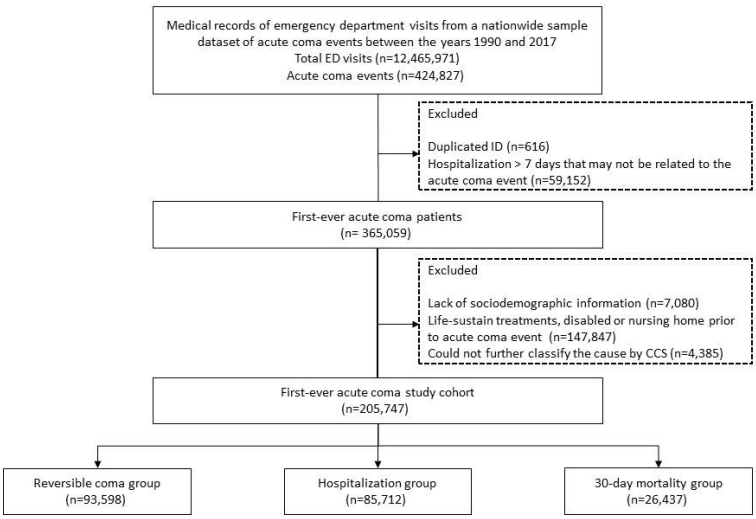

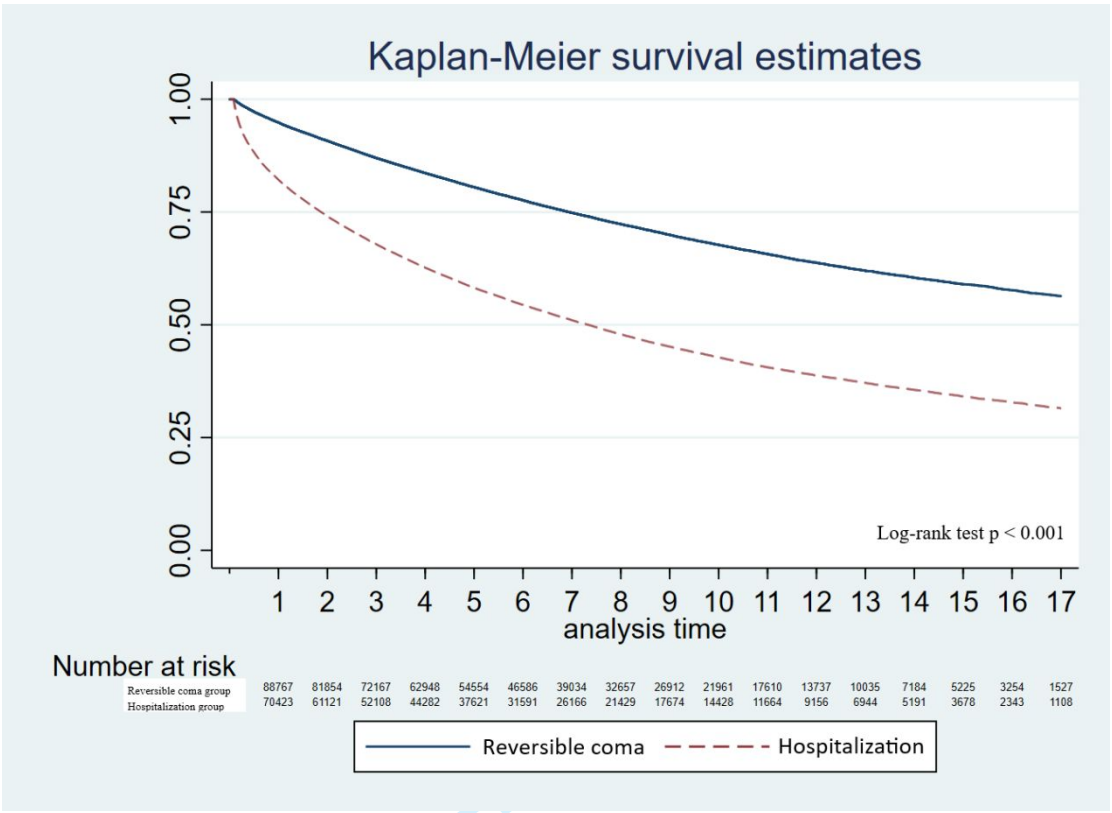

Supplementary Figure 1 Survival analysis of acute coma patients

Supplementary Table 1 Clinical classification software for grouping the causes of acute coma

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Neurological group				
Primary CNS	CNS meningitis	7,76	7,76	Meningitis (except that caused by tuberculosis or sexually transmitted disease),Viral infection
	Brain space occupied	11,35	11,35	Cancer of brain and nervous system,Cancer of head and neck
	CNS encephalitis	77,78,8	77,78,8	Encephalitis (except that caused by tuberculosis or sexually transmitted disease),Other CNS infection and poliomyelitis,Other infections; including parasitic
	Cerebrovascular disease	109,110,111,112,113,82	109,110,111,112,113,82	Acute cerebrovascular disease,Late effects of cerebrovascular disease,Occlusion or stenosis of precerebral arteries,Other and ill-defined cerebrovascular disease,Paralysis,Transient cerebral ischemia
	CNS trauma	227,228,233,234,235	227,228,233,234,235	Crushing injury or internal injury,Intracranial injury,Open wounds of head; neck; and trunk,Skull and face fractures,Spinal cord injury
Encephalopathy	Encephalopathy	79,80,81,84,95	79,80,81,84,95	Headache; including migraine,Multiple sclerosis,Other hereditary and degenerative nervous system conditions,Other nervous system disorders, Parkinson's disease
	Dementia	653	653	Delirium dementia and amnestic and other cognitive disorders,Delirium, dementia, and amnestic and other cognitive disorders
Seizure	Seizure and epilepsy	83	83	Epilepsy; convulsions

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Trauma	Trauma	225,226,229,230,231,232,236,239,240,244,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2612,2618,2619,2620,2621	0,144,145,146,147,148,149,225,226,229,230,231,232,236,239,240,244,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2612,2614,2618,2619,2620,2621	Arthroscopy,Burns,E Codes: Cut/pierceb,E Codes: Drowning/submersion,E Codes: Fall,E Codes: Fire/burn,E Codes: Firearm,E Codes: Machinery,E Codes: Motor vehicle traffic (MVT),E Codes: Other specified and classifiable,E Codes: Other specified; NEC,E Codes: Overexertion,E Codes: Pedal cyclist; not MVT,E Codes: Pedestrian; not MVT,E Codes: Place of occurrence,E Codes: Transport; not MVT,E Codes: Unspecified,External cause codes: Cut/pierce,External cause codes: Drowning/submersion,External cause codes: Fall,External cause codes: Fire/burn,External cause codes: Firearm,External cause codes: Machinery,External cause codes: Motor vehicle traffic (MVT),External cause codes: Other specified and classifiable,External cause codes: Other specified; NEC,External cause codes: Overexertion,External cause codes: Pedal cyclist; not MVT,External cause codes: Pedestrian; not MVT,External cause codes: Place of occurrence,External cause codes: Struck by; against,External cause codes: Transport; not MVT,External cause codes: Unspecified,Fracture of lower limb,Fracture of neck of femur (hip),Fracture of upper limb,Fracture treatment including reposition with or without fixation of other fracture or or dislocation,Fracture treatment including reposition with or without fixation; facial

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				fracture or dislocation,Fracture treatment including reposition with or without fixation; hip or femur fracture or dislocati,Fracture treatment including reposition with or without fixation; lower extremity fracture or disloc,Fracture treatment including reposition with or without fixation; radius or ulna fracture or disloca,Joint disorders and dislocations; trauma-related,Open wounds of extremities,Other fractures,Other injuries and conditions due to external causes,Sprains and strains,Superficial injury; contusion
	Injury and suicide	2615,662	2615,662	E Codes: Suffocation,External cause codes: Suffocation,Suicide and intentional self-inflicted injury
Medical group				
Alcohol	Alcohol	660	660	Alcohol-related disorders
Cardiovascular	Cardiovascular	100,101,102,104,105,106,107,108,114,115,116,117,118,119,121,247,96,97,98,99	100,101,102,104,105,106,107,108,114,115,116,117,118,119,121,183,96,97,98,99	Acute myocardial infarction,Aortic and peripheral arterial embolism or thrombosis,Aortic; peripheral; and visceral artery aneurysms,Cardiac arrest and ventricular fibrillation,Cardiac dysrhythmias,Conduction disorders,Congestive heart failure; nonhypertensive,Coronary atherosclerosis and other heart disease,Essential hypertension,Heart valve disorders,Hypertension complicating pregnancy; childbirth and the puerperium,Hypertension with complications and secondary hypertension,Lymphadenitis,Nonspecific chest pain,Other and ill-defined heart disease,Other circulatory disease,Other

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				diseases of veins and lymphatics,Peri-; endo-; and myocarditis; cardiomyopathy (except that caused by tuberculosis or sexually transm,Peripheral and visceral atherosclerosis,Phlebitis; thrombophlebitis and thromboembolism,Varicose veins of lower extremity
	Shock	249	249	Shock
Diabetes and insulin	Diabetes and insulin	186,49,50	186,49,50	Diabetes mellitus with complications,Diabetes mellitus without complication,Diabetes or abnormal glucose tolerance complicating pregnancy; childbirth; or the puerperium
Digestive	Digestive	120,136,137,138,139,140,141,143,145,146,147,152,153,154,155,250,251	120,136,137,138,139,140,141,143,145,146,147,152,153,154,155,250,251	Abdominal hernia,Abdominal pain,Anal and rectal conditions,Diseases of mouth; excluding dental,Disorders of teeth and jaw,Diverticulosis and diverticulitis,Esophageal disorders,Gastritis and duodenitis,Gastroduodenal ulcer (except hemorrhage),Gastrointestinal hemorrhage,Hemorrhoids,Intestinal obstruction without hernia,Nausea and vomiting,Noninfectious gastroenteritis,Other disorders of stomach and duodenum,Other gastrointestinal disorders,Pancreatic disorders (not diabetes)
	Liver	149,151,222,6	149,151,222,6	Biliary tract disease,Hemolytic jaundice and perinatal jaundice,Hepatitis,Other liver diseases
Drugs	Intoxication	241,242,243,2613,661	241,242,243,2613,661,663	E Codes: Poisoning,External cause codes: Poisoning,Poisoning by nonmedicinal substances,Poisoning by other medications and drugs,Poisoning by

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				psychotropic agents,Screening and history of mental health and substance abuse codes,Substance-related disorders
	Medication	2617	2617	Adverse effects of medical drugs,E Codes: Adverse effects of medical drugs
Electrolyte	Electrolyte	55	55	Fluid and electrolyte disorders
Endocrine	Endocrine	48,51,52,53,58	48,51,52,53,58	Disorders of lipid metabolism,Nutritional deficiencies,Other endocrine disorders,Other nutritional; endocrine; and metabolic disorders,Thyroid disorders
Genitourinary	Urogenital	160,161,162,163, 164,165,166	160,162,163,164,16 5,166,168	Calculus of urinary tract,Genitourinary symptoms and ill-defined conditions,Hyperplasia of prostate,Inflammatory conditions of male genital organs,Inflammatory diseases of female pelvic organs,Other diseases of bladder and urethra,Other diseases of kidney and ureters,Other male genital disorders
Hematology	Hematology	59,60,61,62,63,64	59,60,61,62,63,64	Acute posthemorrhagic anemia,Coagulation and hemorrhagic disorders,Deficiency and other anemia,Diseases of white blood cells,Other hematologic conditions,Sickle cell anemia
Infection	Infection	1,10,122,124,125, 126,135,142,148, 159,2,201,248,3,4 ,5,9,90,92	1,10,122,124,125,1 26,142,148,159,197 ,2,201,246,247,248, 3,4,5,9,90,92	Acute and chronic tonsillitis,Acute bronchitis,Appendicitis and other appendiceal conditions,Bacterial infection; unspecified site,Fever of unknown origin,Gangrene,HIV infection,Immunizations and screening for infectious disease,Infective arthritis and osteomyelitis (except that caused by tuberculosis or sexually transmitted di,Inflammation; infection of eye (except

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				that caused by tuberculosis or sexually transmitteddisease),Intestinal infection,Lymphadenitis,Mycoses,Other upper respiratory infections,Otitis media and related conditions,Peritonitis and intestinal abscess,Pneumonia (except that caused by tuberculosis or sexually transmitted disease),Septicemia (except in labor),Sexually transmitted infections (not HIV or hepatitis),Skin and subcutaneous tissue infections,Tuberculosis,Urinary tract infections
	Influenza	123	123	Influenza
Musculoskeletal and integumentary	Musculosketal	197,198,199,200, 203,204,205,206, 207	173,198,199,200,20 3,204,205,206,207	Chronic ulcer of skin,Osteoarthritis,Osteoporosis,Other diagnostic procedures on skin subcutaneous tissue fascia and breast,Other inflammatory condition of skin,Other non-traumatic joint disorders,Other skin disorders,Pathological fracture,Skin and subcutaneous tissue infections,Spondylosis; intervertebral disc disorders; other back problems
	Connective	144,202,210,211, 253,54,57,86,87,8 8,89,91,94	144,202,210,211,25 3,54,57,86,87,88,89 ,91,94	Allergic reactions,Blindness and vision defects,Cataract,Glaucoma,Gout and other crystal arthropathies,Immunity disorders,Other connective tissue disease,Other ear and sense organ disorders,Other eye disorders,Regional enteritis and ulcerative colitis,Retinal detachments; defects; vascular occlusion; and retinopathy,Rheumatoid arthritis and related disease,Systemic lupus erythematosus and connective tissue

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				disorders
Neoplasm	Malignancy	12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,36,37,38,39,40,41,42,43,44,45,47	12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,36,37,38,39,40,41,42,43,44,45,47	Cancer of bladder,Cancer of bone and connective tissue,Cancer of breast,Cancer of bronchus; lung,Cancer of cervix,Cancer of colon,Cancer of esophagus,Cancer of kidney and renal pelvis,Cancer of liver and intrahepatic bile duct,Cancer of other female genital organs,Cancer of other GI organs; peritoneum,Cancer of other male genital organs,Cancer of other urinary organs,Cancer of ovary,Cancer of pancreas,Cancer of prostate,Cancer of rectum and anus,Cancer of stomach,Cancer of testis,Cancer of thyroid,Cancer of uterus,Cancer; other and unspecified primary,Cancer; other respiratory and intrathoracic, Hodgkin's disease,Leukemias,Maintenance chemotherapy; radiotherapy,Malignant neoplasm without specification of site,Melanomas of skin,Multiple myeloma,Neoplasms of unspecified nature or uncertain behavior, Non-Hodgkin's lymphoma,Other and unspecified benign neoplasm,Other non-epithelial cancer of skin,Secondary malignancies

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
Women's health and perinatal care	Women's health and perinatal care	167,168,169,170, 171,172,173,174, 175,176,177,178, 179,180,181,182, 183,184,185,187, 188,189,190,191, 192,193,194,195, 196,218,220,221, 223,224,46	167,169,170,171,172,173,174,175,176, 177,178,179,180,181,182,184,185,187, 188,189,190,191,192,193,194,195,196, 218,219,220,221,223,224,46	Benign neoplasm of uterus,Birth trauma,Contraceptive and procreative management,Early or threatened labor,Ectopic pregnancy,Endometriosis,Female infertility,Fetal distress and abnormal forces of labor,Fetopelvic disproportion; obstruction,Forceps delivery,Hemorrhage during pregnancy; abruptio placenta; placenta previa,Hypertension complicating pregnancy; childbirth and the puerperium,Induced abortion,Inflammatory diseases of female pelvic organs,Intrauterine hypoxia and birth asphyxia,Liveborn,Malposition; malpresentation,Menopausal disorders,Menstrual disorders,Nonmalignant breast conditions,OB-related trauma to perineum and vulva,Other complications of birth; puerperium affecting management of mother,Other complications of pregnancy,Other female genital disorders,Other perinatal conditions,Other pregnancy and delivery including normal,Ovarian cyst,Polyhydramnios and other problems of amniotic cavity,Postabortion complications,Previous C-section,Prolapse of female genital organs,Prolonged pregnancy,Respiratory distress syndrome,Short gestation; low birth weight; and fetal growth retardation,Spontaneous abortion,Umbilical cord complication
Renal	Renal	156,157,158	156,157,158,161	Acute and unspecified renal

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				failure,Chronic kidney disease,Nephritis; nephrosis; renal sclerosis,Other diseases of kidney and ureters
Respiratory	Respiratory and hypoxia	103,127,128,129, 130,131,132,133, 134,56	103,127,128,129,13 0,131,132,133,134, 135,56	Aspiration pneumonitis; food/vomitus,Asthma,Chronic obstructive pulmonary disease and bronchiectasis,Cystic fibrosis,Intestinal infection,Lung disease due to external agents,Other lower respiratory disease,Other upper respiratory disease,Pleurisy; pneumothorax; pulmonary collapse,Pulmonary heart disease,Respiratory failure; insufficiency; arrest (adult)
Functional group				
Psychiatry	Psychiatry	650,651,652,656, 657,658,659,663, 670	650,651,652,656,65 7,658,659,670	Adjustment disorders,Anxiety disorders,Attention-deficit conduct and disruptive behavior disorders,Attention-deficit, conduct, and disruptive behavior disorders,Impulse control disorders NEC,Impulse control disorders, NEC,Miscellaneous mental health disorders,Mood disorders,Personality disorders,Schizophrenia and other psychotic disorders,Screening and history of mental health and substance abuse codes
Symptomatic and care	Symptomatic and care	246,252,254,255, 256,000,000,000	252,254,255,256,25 7,258,259	Administrative/social admission,Fever of unknown origin,Malaise and fatigue,Medical examination/evaluation,Other aftercare,Other screening for suspected conditions (not mental disorders or infectious disease),Rehabilitation care;

Acute coma causes	Subgroups	ICD-9 CCS groups	ICD-10 CCS groups	Lable
				fitting of prostheses; and adjustment of devices,Residual codes; unclassified
Syncope	Syncope	245,93	245,93	Conditions associated with dizziness or vertigo,Syncope
Others	Iatrogenic	0,237,238,2616	237,238,2616	Adverse effects of medical care,Complication of device; implant or graft,Complications of surgical procedures or medical care,E Codes: Adverse effects of medical care,Invalid procedure
	Congenital	208,209,212,213,214,215,216,217,219,654,655	208,209,212,213,214,215,216,217,654,655	Acquired foot deformities,Cardiac and circulatory congenital anomalies,Developmental disorders,Digestive congenital anomalies,Disorders usually diagnosed in infancy childhood or adolescence,Disorders usually diagnosed in infancy, childhood, or adolescence,Genitourinary congenital anomalies,Nervous system congenital anomalies,Other acquired deformities,Other bone disease and musculoskeletal deformities,Other congenital anomalies,Short gestation; low birth weight; and fetal growth retardation
	Environment	2611	2611	E Codes: Natural/environment,External cause codes: Natural/environment

Supplementary Table 2 Characteristics of acute coma cohort

	Total acute coma n (%)		Reversible coma n (%)		Hospitalization n (%)		30-day mortality n (%)		*p*-value
Total	205,747	(100·00)	93,598	(45·49)	85,712	(41·66)	26,437	(12·85)	<0·001
Sex									
Male	111,897	(54·39)	49,738	(53·14)	46,910	(54·73)	15,249	(57·68)	<0·001
Female	93,850	(45·61)	43,860	(46·86)	38,802	(45·27)	11,188	(42·32)	
Age	58·27	±23·04	39·81	±19·99	52·93	±22·93	70·99	±16·90	<0·001
Age group									
<18	61,756	(30·02)	38,509	(13·56)	19,661	(22·94)	3,586	(13·56)	<0·001
18-64	49,039	(23·83)	22,955	(23·88)	19,771	(23·07)	6,313	(23·88)	
≧65	94,952	(46·15)	32,134	(62·56)	46,280	(53·99)	16,538	(62·56)	
CCI index									
CCI≦1	133,867	(65·06)	73,552	(78·58)	46,694	(54·48)	13,621	(51·52)	<0·001
CCI>1	71,880	(34·94)	20,046	(21·42)	39,018	(45·52)	12,816	(48·48)	
Income									
Low	58,488	(28·43)	26,255	(28·05)	25,054	(29·23)	7,179	(27·15)	<0·001
Middle	73,869	(35·90)	35,899	(38·35)	29,228	(34·10)	8,742	(33·07)	
High	73,390	(35·67)	31,444	(33·60)	31,430	(36·67)	10,516	(39·78)	
Occupation									
Dependents of the insured individuals	62,271	(30·27)	27,616	(29·50)	26,700	(31·15)	7,955	(30·09)	<0·001
Civil servants, teachers, military, veterans	2,915	(1·42)	1,429	(1·53)	1,151	(1·34)	335	(1·27)	
Nonmanual workers and professionals	20,121	(9·78)	11,891	(12·70)	6,401	(7·47)	1,829	(6·92)	
Manual workers	72,036	(35·01)	29,707	(31·74)	31,824	(37·13)	10,505	(39·73)	
Other	48,404	(23·53)	22,955	(24·53)	19,636	(22·91)	5,813	(21·99)	
Urbanization									
Urban	83,476	(40·57)	41,892	(44·76)	31,882	(37·20)	9,702	(36·70)	<0·001
Suburban	76,632	(37·25)	33,150	(35·42)	33,456	(39·03)	10,026	(37·92)	
Rural	45,639	(22·18)	18,556	(19·82)	20,374	(23·77)	6,709	(25·38)	
Causes of acute coma									<0·001
Neurological cause group	56,790	(27·60)	22,153	(23·67)	24,430	(28·50)	10,207	(38·61)	<0·001
CNS	30,065	(14·61)	8,183	(8·74)	14,639	(17·08)	7,243	(27·40)	
Encephalopathy	6,700	(3·26)	2,616	(2·79)	3,573	(4·17)	511	(1·93)	
Seizure	2,225	(1·08)	1,157	(1·24)	1,020	(1·19)	48	(0·18)	
Trauma	17,800	(8·65)	10,197	(10·89)	5,198	(6·06)	2,405	(9·10)	
Medical cause group	137,330	(66·75)	65,158	(69·61)	57,007	(66·51)	15,165	(57·36)	
Alcohol	2,533	(1·23)	2,255	(2·41)	257	(0·30)	21	(0·08)	
Cardiovascular	19,367	(9·41)	7,938	(8·48)	8,148	(9·51)	3,281	(12·41)	
Diabetes and insulin	11,155	(5·42)	4,178	(4·46)	5,529	(6·45)	1,448	(5·48)	
Digestive	19,904	(9·67)	9,364	(10·00)	7,968	(9·30)	2,572	(9·73)	
Drugs	5,036	(2·45)	2,002	(2·14)	1,941	(2·26)	1,093	(4·13)	
Electrolyte	456	(0·22)	249	(0·27)	152	(0·18)	55	(0·21)	
Endocrine	2,427	(1·18)	1,086	(1·16)	904	(1·05)	437	(1·65)	
Genitourinary	3,463	(1·68)	1,836	(1·96)	1,327	(1·55)	300	(1·13)	
Hematology	587	(0·29)	292	(0·31)	228	(0·27)	67	(0·25)	
Infection	31,063	(15·10)	14,714	(15·72)	14,005	(16·34)	2,344	(8·87)	
Musculoskeletal and integumentary	6,144	(2·99)	3,659	(3·91)	2,208	(2·58)	277	(1·05)	
Neoplasm	10,062	(4·89)	3,938	(4·21)	4,459	(5·20)	1,665	(6·30)	
Renal	3,564	(1·73)	1,149	(1·23)	1,884	(2·20)	531	(2·01)	
Respiratory	9,419	(4·58)	3,550	(3·79)	5,007	(5·84)	862	(3·26)	
Women's health and perinatal care	12,150	(5·91)	8,948	(9·56)	2,990	(3·49)	212	(0·80)	
Functional cause group	11,627	(5·65)	6,287	(6·72)	4,275	(4·99)	1,065	(4·03)	
Psychiatry	4,765	(2·32)	2,923	(3·12)	1,827	(2·13)	15	(0·06)	
Symptoms	1,379	(0·67)	881	(0·94)	342	(0·40)	156	(0·59)	
Syncope	521	(0·25)	352	(0·38)	169	(0·20)	0	(0·00)	
Others	4,962	(2·41)	2,131	(2·28)	1,937	(2·26)	894	(3·38)	
Outcome									
ICU	54,614	(26·54)	0	(0·00)	39,144	(45·67)	15,470	(58·52)	<0·001
LSTs	84,538	(41·09)	10,578	(11·30)	50,056	(58·40)	23,904	(90·42)	<0·001
Rehab	29,273	(14·23)	4,816	(5·15)	23,728	(27·68)	729	(2·76)	<0·001
Nursing home	3,861	(1·88)	492	(0·53)	3,261	(3·80)	108	(0·41)	<0·001
Disable	13,514	(6·57)	2,856	(3·05)	10,629	(12·40)	29	(0·11)	<0·001

CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department;

ICU: intensive care units; LST: life-sustaining treatment;

Chi-Square Test analyzed category variables distribution among groups; continue variable by One-way ANOVA·

Supplementary Table 3 Generalized linear model analysis of acute coma patients

		Reversible coma v.s. 30-day mortality				Hospitalization v.s. 30-day mortality			
		OR (95%CI)	*p*-value	aOR (95%CI)	*p*-value	OR (95%CI)	*p*-value	aOR (95%CI)	*p*-value
Sex	Male vs Female	1·20 (1·17-1·23)	<0·0001	1·29 (1·25-1·33)	<0·0001	1·13 (1·10-1·16)	<0·0001	1·14 (1·10-1·17)	<0·0001
Age	19-64 vs ≤ 18 years old	0·34 (0·32-0·35)	<0·0001	0·44 (0·42-0·46)	<0·0001	0·57 (0·55-0·60)	<0·0001	0·59 (0·56-0·62)	<0·0001
	≥ 65 vs ≤ 18 years old	0·18 (0·17-0·19)	<0·0001	0·26 (0·25-0·27)	<0·0001	0·52 (0·49-0·53)	<0·0001	0·44 (0·42-0·46)	<0·0001
CCI	> 1 vs ≤ 1	0·29 (0·28-0·30)	<0·0001	0·44 (0·42-0·45)	<0·0001	0·88 (0·87-0·91)	<0·0001	1·04 (1·01-1·07)	0·0219
Income	Middle vs low group	1·22 (1·18-1·26)	<0·0001	1·58 (1·52-1·64)	<0·0001	1·17 (1·13-1·21)	<0·0001	1·30 (1·25-1·35)	<0·0001
	High vs low group	1·37 (1·33-1·42)	<0·0001	1·33 (1·28-1·37)	<0·0001	1·12 (1·08-1·16)	<0·0001	1·12 (1·09-1·17)	<0·0001
Occupation	Dependents of the insured individuals vs others	0·82 (0·72-0·92)	0·0012	0·83 (0·73-0·95)	0·0055	0·99 (0·87-1·11)	0·7416	0·94 (0·83-1·07)	0·3469
	Civil servants, teachers, military, veterans vs others	1·53 (1·34-1·74)	<0·0001	0·93 (0·81-1·07)	0·3002	1·03 (0·89-1·16)	0·774	0·84 (0·74-0·97)	0·0136
	Nonmanual workers and professionals vs others	0·67 (0·59-0·75)	<0·0001	0·84 (0·74-0·96)	0·0084	0·88 (0·78-1·00)	0·0503	0·89 (0·78-1·01)	0·0799
	Manual workers vs others	0·93 (0·82-1·05)	0·2501	1·04 (0·91-1·18)	0·6073	0·99 (0·87-1·12)	0·8258	1·01 (0·89-1·15)	0·8776
Urbanization	Urban	0·77 (0·74-0·79)	<0·0001	0·83 (0·80-0·86)	<0·0001	1·01 (0·98-1·05)	0·3561	1·05 (1·01-1·08)	0·0064
	Urbanization	0·64 (0·62-0·66)	<0·0001	0·77 (0·74-0·80)	<0·0001	0·93 (0·89-0·96)	<0·0001	0·98 (0·94-1·02)	0·2124
Causes of coma	**Neurological group**	0·37 (0·34-0·39)	<0·0001	0·55 (0·51-0·59)	<0·0001	0·60 (0·56-0·64)	<0·0001	0·70 (0·65-0·75)	<0·0001
	CNS	0·47 (0·44-0·52)	<0·0001	0·68 (0·62-0·74)	<0·0001	0·99 (0·96-1·02)	0·1051	1·09 (1·00-1·19)	0·0517
	Encephalopathy	2·15 (1·90-2·43)	<0·0001	4·08 (3·59-4·63)	<0·0001	3·21 (2·86-3·65)	<0·0001	4·24 (3·75-4·80)	<0·0001
	Seizure	10·11 (7·50-13·64)	<0·0001	8·32 (6·15-11·24)	<0·0001	9·47 (7·07-13·24)	<0·0001	9·01 (6·67-12·17)	<0·0001
	Trauma	1·78 (1·63-1·95)	<0·0001	1·75 (1·59-1·92)	<0·0001	1·00 (0·91-1·10)	0·9585	1·02 (0·92-1·11)	0·7595
	Medical group	0·73 (0·68-0·78)	<0·0001	1·39 (1·30-1·49)	<0·0001	0·94 (0·87-1·00)	0·0641	1·16 (1·09-1·25)	<0·0001
	Alcohol	45·05 (29·11-69·72)	<0·0001	33·8 (21·81-52·38)	<0·0001	5·65 (3·60-8·88)	<0·0001	5·20 (3·31-8·17)	<0·0001
	Cardiovascular	1·02 (0·93-1·11)	0·7406	2·04 (1·86-2·24)	<0·0001	1·15 (1·05-1·25)	0·0027	1·50 (1·37-1·65)	<0·0001
	Diabetes and insulin	1·21 (1·10-1·34)	0·0001	3·13 (2·82-3·47)	<0·0001	1·76 (1·60-1·94)	<0·0001	2·31 (2·09-2·55)	<0·0001
	Digestive	1·53 (1·40-1·67)	<0·0001	2·53 (2·31-2·78)	<0·0001	1·43 (1·31-1·57)	<0·0001	1·69 (1·54-1·85)	<0·0001
	Drugs	0·77 (0·69-0·86)	<0·0001	0·72 (0·65-0·81)	<0·0001	0·82 (0·74-0·91)	0·0003	0·82 (0·73-0·91)	0·0003
	Electrolyte	1·90 (1·40-2·57)	<0·0001	2·96 (2·17-4·04)	<0·0001	1·28 (0·93-1·75)	0·1342	1·53 (1·11-2·11)	0·0091
	Endocrine	1·04 (0·91-1·19)	0·5473	1·49 (1·29-1·72)	<0·0001	0·96 (0·83-1·10)	0·5139	1·15 (1·00-1·32)	0·0521
	Genitourinary	2·57 (2·22-2·97)	<0·0001	4·41 (3·80-5·12)	<0·0001	2·04 (1·76-2·37)	<0·0001	2·59 (2·23-3·01)	<0·0001
	Hematology	1·83 (1·39-2·41)	<0·0001	2·53 (1·90-3·36)	<0·0001	1·57 (1·18-2·09)	0·0018	1·83 (1·38-2·44)	<0·0001
	Infection	2·63 (2·41-2·88)	<0·0001	4·26 (3·88-4·67)	<0·0001	2·76 (2·52-3·02)	<0·0001	3·36 (3·07-3·69)	<0·0001
	Musculoskeletal and integumentary	5·54 (4·79-6·41)	<0·0001	8·16 (7·04-9·47)	<0·0001	3·68 (3·17-4·27)	<0·0001	4·35 (3·75-5·05)	<0·0001
	Neoplasm	0·99 (0·90-1·09)	0·8747	2·06 (1·86-2·28)	<0·0001	1·24 (1·12-1·36)	<0·0001	1·57 (1·42-1·73)	<0·0001
	Renal	0·91 (0·80-1·03)	0·142	2·30 (2·01-2·62)	<0·0001	1·64 (1·45-1·86)	<0·0001	2·21 (1·95-2·51)	<0·0001
	Respiratory	1·73 (1·55-1·93)	<0·0001	3·54 (3·16-3·96)	<0·0001	2·68 (2·41-2·98)	<0·0001	3·57 (3·20-3·98)	<0·0001
	Women's health and perinatal care	17·71 (15·13-20·72)	<0·0001	11·86 (10·11-13·92)	<0·0001	6·51 (5·55-7·64)	<0·0001	5·44 (4·63-6·40)	<0·0001
	Functional group	(ref· of coma group)							
	Psychiatry	81·68 (48·90-136·46)	<0·0001	57·02 (34·11-95·33)	<0·0001	56·13 (33·69-93·92)	<0·0001	48·29 (28·88-80·77)	<0·0001
	Symptoms	2·37 (1·97-2·86)	<0·0001	2·78 (2·30-3·38)	<0·0001	1·01 (0·82-1·24)	0·9106	1·11 (0·90-1·37)	0·3158
	Syncope	NC		NC		NC		NC	
	Others	(ref of causes of coma)							

aOR: adjusted odds ratio; CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department; ICU: intensive care units; LST: life-sustaining treatment;

Syncope: no convergence

Supplementary Table 4 Characteristics of acute coma hospitalization within 14 days

	Total acute coma		Acute coma						
			Reversible coma		Hospitalization		30-day mortality		
	n	(%)	n	(%)	n	(%)	n	(%)	*p*-value
Total	231,516	(100·00)	65,711	(28·38)	50,636	(21·87)	11,5169	(49·75)	<0·001
Sex									
Male	125,340	(54·14)	34,157	(51·98)	27,705	(54·71)	63,478	(55·12)	<0·001
Female	106,176	(45·86)	31,554	(48·02)	22,931	(45·29)	51,691	(44·88)	
Age	60·08	±22·53	46·51	±21·33	52·26	±22·72	71·27	±16·65	<0·001
Age group									
<18	61,620	(26·62)	32,542	(49·52)	18,623	(36·78)	10,455	(9·08)	<0·001
18-64	54,757	(23·65)	18,393	(27·99)	14,918	(29·46)	21,446	(18·62)	
≧65	115,139	(49·73)	14,776	(22·49)	17,095	(33·76)	83,268	(72·30)	
CCI index									
CCI≦1	142,468	(61·54)	55,558	(84·55)	34,629	(68·39)	52,281	(45·40)	<0·001
CCI>1	89,048	(38·46)	10,153	(15·45)	16,007	(31·61)	62,888	(54·60)	
Income									
Low	77,350	(33·41)	17,393	(26·47)	13,002	(25·68)	46,955	(40·77)	<0·001
Middle	82,140	(35·48)	23,532	(35·81)	19,238	(37·99)	39,370	(34·19)	
High	72,026	(31·11)	24,786	(37·72)	18,396	(36·33)	28,844	(25·04)	
Occupation									
Dependents of the insured individuals	72,965	(31·52)	19,801	(30·13)	16,415	(32·42)	36,749	(31·91)	<0·001
Civil servants, teachers, military personnel, veterans	2,974	(1·28)	994	(1·51)	703	(1·39)	1,277	(1·11)	
Nonmanual workers and professionals	20,109	(8·69)	10,048	(15·29)	5,478	(10·82)	4,583	(3·98)	
Manual workers	82,064	(35·45)	19,267	(29·32)	16,492	(32·57)	46,305	(40·21)	
Other	53,404	(23·07)	15,601	(23·74)	11,548	(22·81)	26,255	(22·80)	
Urbanization									
Urban	156,602	(67·64)	48,471	(73·76)	34,912	(68·95)	73,219	(63·58)	<0·001
Suburban	71,024	(30·68)	16,143	(24·57)	14,815	(29·26)	40,066	(34·79)	
Rural	3,890	(1·68)	1,097	(1·67)	909	(1·80)	1,884	(1·64)	
Causes of coma									<0·001
Neurological group	75,399	(32·57)	20,542	(27·24)	26,165	(34·71)	28,692	(38·05)	<0·001
CNS	41,353	(54·85)	5,237	(25·49)	18,248	(69·74)	17,868	(62·28)	
Encephalopathy	9,753	(12·94)	2,015	(9·81)	1,728	(6·60)	6,010	(20·95)	
Seizure	4,053	(5·38)	2,184	(10·63)	1,466	(5·60)	403	(1·40)	
Trauma	20,240	(26·84)	11,106	(54·06)	4,723	(18·05)	4,411	(15·37)	
Medical group	141,892	(61·29)	36,644	(25·83)	21,244	(14·97)	84,004	(59·20)	
Alcohol	7,260	(5·12)	6,650	(18·15)	389	(1·83)	221	(0·26)	
Cardiovascular	20,753	(14·63)	3,152	(8·60)	1,686	(7·94)	15,915	(18·95)	
Digestive	17,023	(12·00)	3,111	(8·49)	1,896	(8·92)	12,016	(14·30)	
DM & Insulin	17,795	(12·54)	4,933	(13·46)	2,425	(11·41)	10,437	(12·42)	
Drugs	8,362	(5·89)	2,594	(7·08)	2,149	(10·12)	3,619	(4·31)	
Electrolyte	813	(0·57)	421	(1·15)	104	(0·49)	288	(0·34)	
Endocrine	3,439	(2·42)	1,362	(3·72)	762	(3·59)	1,315	(1·57)	
Genitourinary	1,302	(0·92)	178	(0·49)	116	(0·55)	1,008	(1·20)	
Hematology	678	(0·48)	256	(0·70)	124	(0·58)	298	(0·35)	
Infection	24,906	(17·55)	2,723	(7·43)	5,558	(26·16)	16,625	(19·79)	
Musculoskeletal and integumentary	2,301	(1·62)	588	(1·60)	507	(2·39)	1,206	(1·44)	
Neoplasm	9,804	(6·91)	222	(0·61)	249	(1·17)	9,333	(11·11)	
Renal	4,108	(2·90)	131	(0·36)	342	(1·61)	3,635	(4·33)	
Respiratory	10,968	(7·73)	1,421	(3·88)	2,019	(9·50)	7,528	(8·96)	
Women's health and perinatal care	12,380	(8·72)	8,902	(24·29)	2,918	(13·74)	560	(0·67)	
Functional group	14,225	(6·14)	8,525	(59·93)	3,227	(22·69)	2,473	(17·38)	
Psychiatry	5,665	(39·82)	3,008	(35·28)	2,545	(78·87)	112	(4·53)	
Symptoms	5,775	(40·60)	4,766	(55·91)	257	(7·96)	752	(30·41)	
Syncope	785	(5·52)	612	(7·18)	173	(5·36)	0	(0·00)	
Others	2,000	(14·06)	139	(1·63)	252	(7·81)	1,609	(65·06)	
Outcome									
ICU	56,648	(28·28)	327	(0·58)	40,207	(70·97)	16,114	(28·45)	<0·001
LST	161,924	(69·94)	59,493	(36·74)	22,722	(14·03)	79,709	(49·23)	<0·001
Rehab	108,716	(46·96)	56,008	(51·52)	12,798	(11·77)	39,910	(36·71)	<0·001
Disable	13,797	(5·96)	1,379	(9·99)	4,972	(36·04)	7,446	(53·97)	<0·001
Nursing case	5,145	(2·22)	139	(2·70)	941	(18·29)	4,065	(79·01)	<0·001

CCI: Charlson Comorbidity Index; CI: confidence interval; CNS: central nervous system; ED: emergency department; ICU: intensive care units; LST: life-sustaining treatment;

Chi-Square Test analyzed category variables distribution among groups; continue variable by One-way ANOVA·