Circadian Variations in the Occurrence of Intracerebral Hemorrhage from Different Sources of Income: A Hospital-Based Cross-Sectional Study

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Circadian Variations in the occurrence of Intracerebral Hemorrhage from different sources of income: A Hospital-Based Cross-sectional Study

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Abstract

Background: The onset time of intracerebral hemorrhage (ICH) may be closely related to the working style and living habits of people, which are determined by different income sources in China. Therefore, our purpose was to investigate the Circadian Variations in the occurrence of ICH from different sources of income.

Methods: This retrospective study enrolled 4,327 patients with ICH. Based on the time of a day at which the patients developed symptoms, the classifiable onset time was assigned to one of eight three-hour intervals. And based on different income sources, they were categorized into three groups: Farmers, Wage-earners and Freelancers. Characteristics and risk factors of patients were then summarized, and the circadian variation of three groups of patients' known time of onset and those stratified by gender and age were analyzed.

Results: The frequency of ICH onset exhibited significant circadian variation among the three income groups, demonstrating a bimodal distribution in the daytime, with a nadir during the night (all $P < 0.001$). Three groups showed a significant initial peak between 06:01 and 09:00, with a smaller second peak that between 15:01 and 18:00 for Farmers and Wage-earners and 18:01 and 21:00 for Freelancers. After stratification by gender and age, all demonstrated a bimodal distribution except women in Wage-earners and under 65 years of age in Wage-earners.

Conclusions: Different circadian variations of ICH onset time were found in patients with different income sources in southwest China's Chongqing Municipality cohort. Moreover, the frequency and distribution pattern of peak hours were closely related to the working style and living habits of people with different income sources.

Keywords: Intracerebral hemorrhage, Circadian variations, Income sources, Risk factors

Background

Primary intracerebral hemorrhage (ICH) is a common, devastating disease that lacks an effective treatment and is associated with a high rate of death or disability [1-4]. Evidence from epidemiological studies on worldwide stroke victims have indicated that the overall incidence of ICH had been roughly stable at 24.6 per 100,000 person-years, yet the rate has increased to 51.8 in Asian populations [3]. Moreover, the National Epidemiology Survey of Stroke in China (NESS-China) reported that 66.2 out of every 100,000 people suffered from ICH in 2012 to 2013, and the greatest stroke burden was observed in rural areas of northern regions [5].

For nearly 30 years, circadian variation of first-ever ICH has been widely investigated around the world [6-22] (Table 1). Nevertheless, the findings in many community- and hospital-based studies were variable or even contradictory. Numerous studies have demonstrated that ICH mostly first occurred in the morning hours [6-14, 20-21], and some of which were accompanied by a second peak [6-9,20]. Several researchers have also found the peak occurs between morning and afternoon [17, 22] or awake [18-19]. Furthermore, two additional studies with 527 patients in Asia reported that a single peak was observed in the afternoon hours [15-16]. In these studies, circadian variation of ICH incidence may be depended on the methodology used. They divided a day into 2-[6-9,15,21], 3-[20], 4-[11], 6-[10, 12-14,16], 8-hour intervals [17,22] or more [18-19]. The different findings concerning the time intervals of statistically significant ICH incidence were identified as: a morning peak (06:00-08:00 h [6], 08:00-10:00 h [7-8], 08:00-12:00 h [11], 10:00-12:00 h [9], 06:00-12:00 h [10, 12-14]), sometimes with a second peak (16:00-18:00 h [7] and 18:00-20:00 h [6,8-9]), or a single peak during the afternoon (18:00-20:00 h [15], 12:00-18:00 [16]), or a single peak from morning to afternoon (08:00-16:00 h [17]), or an awake peak [18-19]. Not only the methodology, the exact peak circadian variation of ICH incidence also depended on gender, age, and living habits [15,20].

China is a large agricultural country. Although the urban population has been growing rapidly with continuous urbanization, the population of farmers still numbers nearly 600 million. Farmers' income mainly comes from agricultural production, while for urban population, their main sources of income are wages and non-fixed income. People with different income sources differ in working style and living habits, and these factors may be related to the circadian variations in the occurrence of ICH.

Therefore, our aim was to investigate circadian variations in the occurrence of ICH from different sources of income, as well as observe whether the onset time of ICH was affected by the traditional risk factors.

Methods

Study population

This cross-sectional study was approved by the ethics committee of the University-Town Hospital Affiliated to Chongqing University of Medical Sciences. We screened 4,327 patients with ICH from databases of University-Town Hospital Affiliated to Chongqing University of Medical Sciences and Affiliated Three Gorges Hospital of Chongqing University (including Neurological Department, Neurosurgery, First aid Branch, Baian Branch and Yuan Branch) from January 1, 2012 to December 31, 2017. All patients underwent complete cranial computed tomography (CT) scans and/or magnetic resonance imaging (MRI) within 24 hours after symptoms onset. The diagnosis of ICH was confirmed by local neurologists and/or neurosurgeons based on the standards of the literature [23]. We exclude cases involving traumatic ICH, subarachnoid hemorrhages (SAH) and those with a history of ICH. All the variables including gender, age, occupation, income source, date and hour of onset, situation at onset, health-related behaviors and past medical history were recorded. we divided the patients into three groups based on the different income sources: i.e. Farmers, Wage-earners and Freelancers. Among these, 2,245 were Farmers (whose income mainly came from agricultural production), 1,231 were Wage-earners (whose income mainly came from wages) and 851 were Freelancers (whose income were unfixed).

Data analysis

Based on the data provided by the medical records, the classifiable onset time was assigned to one of eight three-hour intervals: 00:01-03:00; 03:01-06:00; 06:01-09:00; 09:01-12:00; 12:01-15:00; 15:01-18:00; 18:01-21:00; 21:01-24:00 hours. In addition to the previous stated criteria for exclusion, we omit cases in which exact hours or approximate time intervals of onset could not be determined. All analyses were performed on the eight onset-time partitions further divided into the three different income sources, gender and age groups. To examine the effect of age on the time of onset, the patients were stratified into < 65 and ≥ 65 years. The relative risk factors of ICH in different income source groups were assessed as follows. Hypertension（HTN）was defined as those with an average (calculated from three measurements) systolic pressure (SBP) ≥ 140 mmHg and/or an average diastolic blood pressure (DBP) ≥ 90 mmHg, a history of hypertension, or prior use of antihypertensive agents. However, cases of prehypertension (PHT, representing a SBP of 120-139 mmHg and/or a DBP of 80-89 mmHg) were not included [24]. Dyslipidemia was defined as to be those with total cholesterol (TC) ≥ 5.2 mmol/L, triglyceride (TG) ≥ 1.7 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥ 3.4 mmol/L [25], or the current use of anti - lipidemic medication. Diabetes mellitus (DM) was defined to be the cases with a history of DM or fasting blood glucose (FPG) level ≥ 7.0 mmol/L [26]. The variable Alcohol Consumption is defined to be those that self-reported consuming alcohol more than three times per week. Smoking was defined as current regular use (any amount).

Statistical analyses

All analyses were carried out with SPSS version 24.0 software (IBM Inc., Amonk, NY). Characteristics， risk factors, and age were respectively expressed as mean ± standard deviation while other variables are shown as percentages. Analysis of variance was used for age comparison among three groups, and the Bonferroni method was used for pairwise comparison between groups, where the differences were considered statistically significant when $P < 0.05$. Moreover, the comparison of the rate and composition of the three groups of patients was carried out by the chi-squared test, and the pairwise comparison between the three groups was carried out by the zonal chi-squared method, which was considered statistically significant when $P < 0.017$. The number of cases in each group of different income sources was stratified by time intervals, age, and gender, the differences were subsequently calculated respectively. Assuming that time of day has no effect on the onset of ICH, we should observe a roughly uniform distribution. The frequency of observed cases in each 3-hour interval over 24 hours was compared to the expected frequency using χ^2 goodness-of-fit to determine if the empirical data differed significantly from the expected. In this test, a P-value < 0.05 was considered statistically significant. To estimate the relative risks (RR) with 95% confidence intervals (CI) of ICH occurring at specific time periods respectively, the observed onset case numbers of each group was compared with the average number of 8 3-h intervals.

Results

Patient characteristics

Table 2 shows the demographics and risk factors of all patients afflicted with their first ICH in Farmers, Wage-earners and Freelancers, including those observations in which onset time data was missing. There were significant differences in the gender ratio among three income source groups, when we compared, and significant differences also observed in the comparison of age distribution ratios (all $P < 0.017$). For risk factors, we observed the Wage-Earners group had the highest proportions of heavy drinkers, smokers, dyslipidemia, and DM. There was no significant difference in the proportion of hypertensive patients among three groups, while the proportion of patients with dyslipidemia, diabetes, alcohol consumption and smoking exhibited a variety of differences.

Income sources and circadian variations

Table 3 shows the distributions and statistical results of known and unknown time of onset of the patients with ICH in Farmers, Wage-earners and Freelancers. Of the 4,327 patients, 4,150 provided their time of onset: 2,126 for Farmers, 1,194 for Wage-earners and 830 for Freelancers. The remaining 177 (about 4％) patients with no identifiable times of onset were excluded from further analysis. The circadian variations of three groups exhibited a stark initial peak between 06:01 and 09:00, and a smaller second peak between 15:01 and 18:00 for Farmers and Wage-earners and 18:01 and 21:00 for Freelancers, with a nadir during night (all $P < 0.001$) (Fig. 1).

Stratified by gender and age

Table 4 shows the distributions and statistical results of known and unknown onset time of the patients with ICH stratified by gender in Farmers, Wage-earners and Freelancers. Except women in Wage-earners, the circadian variations of onset time were bimodal in all cases; there is one significant initial peak during the period of 06:01-09:00, a smaller second peak during 15:01-18:00 or 18:01-21:00, and a nadir during the night. (all $P < 0.001$). However, women in Wage-earners exhibited a unimodal pattern, which was between 15:01 and 18:00 (Fig. 2).

Table 5 shows the distributions and statistical results of known and unknown onset time of the patients with ICH stratified by age in Farmers, Wage-earners and Freelancers. Besides a single peak between 06:01 and 09:00 for the group under 65 years of age in Wage-earners, all others exhibited a bimodal distribution with peaks occurring during the daytime (06:01-21:00) (Fig. 3).

Discussion

We investigated the circadian patterns of more than 4,000 patients with ICH from different income sources. To our knowledge, this is the largest study of circadian variation of onset times of ICH available in the literature so far.

The present study showed a significant morning peak between 06:01 and 09:00 in three different income groups as well as in those categories further stratified by gender and age. The only demographic that deviated from this patten was women in Wage-earners. This earlier morning peak was similar to the finding by Omama et al [6] and consistent with the striking rise of blood pressure (BP) for 2 to 3 hours after awakening [27]. The aforementioned papers observed that it is more common that ICH attacks in the morning hours than any other time of the day. They attribute this to a complex interaction of many factors, with the result that a sudden increase in BP emerging as an explanation for this pattern of onset [6-14, 19-22]. Metoki et al [28] found that the risk of hemorrhagic stroke would be increased only when the morning mean SBP soared by more than one-fifth (≥ 25 mmHg), regardless of nocturnal blood pressure patterns. The risk of ICH was also exacerbated by extreme drops in SBP (≥ 20 mmHg nocturnal decline in SBP from the diurnal level). Some authors have comprehensively analyzed the endogenous and exogenous factors which influence morning BP surge [29-30]. A report studied by Morris et al that observed 14 healthy, sedentary, nonsmoking, nonobese, and normotensive men (aged 19-50 years) also indicated that the morning BP increase was attenuated during bed rest, suggesting that the adoption of an upright posture and/or physical activity in the morning contributes to the morning BP surge [31]. While other studies have found that [subject] may be related to underlying diseases and sub-health factors such as hypertension itself [32], DM [33], hyperlipemia [34-35] and dyssomnia [36]. Furthermore, racial differences also affected morning BP surge [37]. In the existing literature, alcohol intake has been identified as a significant risk factor for ICH. It was reported that people who had heavy alcohol intake (alcohol intake ≥ 46 g/d) had higher BP in the morning and increased the risk of stroke, especially hemorrhagic stroke [38-39]. In our findings, we observe that the Wage-Earners group had the highest proportions of heavy drinkers, smokers, dyslipidemia, and DM, but the morning peak was in accord with the others. It seems that none of the common risk factors correlates alone with the morning BP surge of ICH occurrence but it may have a closer tie with physical and/or emotional activity after waking.

Research revealed that nearly 40% of Chinese residents tend to take a nap during the afternoon [40]. Spengos et al. considered the close relationship between the later afternoon peak of onset of ICH and afternoon sleep, the siesta [7]. Wage-earners and Farmers have relatively fixed work schedules, and they also have a habit of taking a siesta. Therefore, they exhibited a pronounced afternoon peak. On the contrary, Freelancers usually do not have a fixed schedule and the habit of taking a siesta due to their irregular working hours, so they didn’t display a same peak distribution pattern in the afternoon as Wage-earners and Farmers.

When analyses were performed by dividing the patients according to gender and age, there were partial differences in the afternoon peak, which was consistent with the findings of Inagawa T et al [8,15]. Combined with the traditional customs and contemporary national conditions of China, we considered that this may be related to the different labor conditions of different groups, family role positioning and so on. Liu et al found that SBP increased significantly in the later half of long working hours, indicating that the risk of ICH may be related to intensity and time of working [41-42]. Women in Farmers and Freelancers mainly take the responsibilities of household chores as a traditional role in the family, including buying groceries and cooking, etc. They will continue to perform housework after finishing work in the afternoon. This could explain their earlier evening peak . Women in Wage-earners are less traditional about their role in the home, seeing themselves as breadwinners and working like men. They are consequently less likely to be a homemaker after working hours. As a result, both men and women in Wage-earners exhibited the same peak distribution pattern in the afternoon. There was no significant difference in working style for Farmers whether they were young or old, so there was no significant difference in the afternoon peak when comparing the two age categories. However, for Wage-earners 65 years or older, they are generally retired and do not work, this may be why they are different from Wage-earners younger than 65 years in the afternoon peak time.

Our study has certain limitations apart from the inherent limitation of the retrospective design. First, this study is based on data from hospitals. This sampling bias means that the data excludes those who were not admitted, who died before admission, and who were not seen by the Department of Medicine. This hospital-based study may have underestimated the true incidence of ICH in the community. Second, even for patients who provided a time of ICH onset, they may have only been estimating due of the factors sleeping, unconsciousness, and being outdoors. Third, more information on the specific nature of the patient's work, hours worked and income, living habits was not collected，so some of the results cannot be well explained, such as why there was no morning peak for women in Wage-earners. These limitations may have confounded the study results.

Conclusions

Our study preliminary demonstrated the circadian variations of ICH onset time in patients with different income sources in southwest China's Chongqing Municipality cohort. These appearances are in accordance with the daily life characteristics of the local people and the routines among the people of different income sources. Although one or more peak hours can be found in ICH onset time in a day, the frequency and distribution pattern of peak hours were closely related to the working style and living habits of people with different income sources. Therefore, we speculate that the work-life rhythm may be a very important factor affecting the onset time of ICH, this may provide the basis for a larger scope of investigation in the future, and provide the possibility for further research on how the work-life rhythm affect the onset time of ICH specific mechanism. Meanwhile, recognition of these particular circadian patterns in ICH is important in planning preventive and control strategies for the sudden, catastrophic cerebrovascular events.

Abbreviations

ICH: intracerebral hemorrhage; NESS-China: National Epidemiology Survey of Stroke in China; CT: computed tomography; MRI: magnetic resonance imaging; SAH: subarachnoid hemorrhages; HTN: Hypertension; SBP: systolic pressure; DBP: diastolic blood pressure; PHT: prehypertension; TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; DM: diabetes mellitus; FPG: fasting blood glucose; RR: relative risks; CI: confidence intervals; BP: blood pressure

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Authors’ contributions

YYW:contributed to the design, interpretation of the data and drafted the manuscript; YYW, EYW and YTP: contributed to the data collection of the study; NY and EYW:performed the statistical analysis; YYW and YTP: contributed to interpreting results, reviewing the manuscript and approved the final version of the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Ethics approval and consent to participate

Ethical approval for the study was obtained from the Institutional Review Board of University-Town Hospital of

Chongqing Medical University. Written informed consent was obtained from participants in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

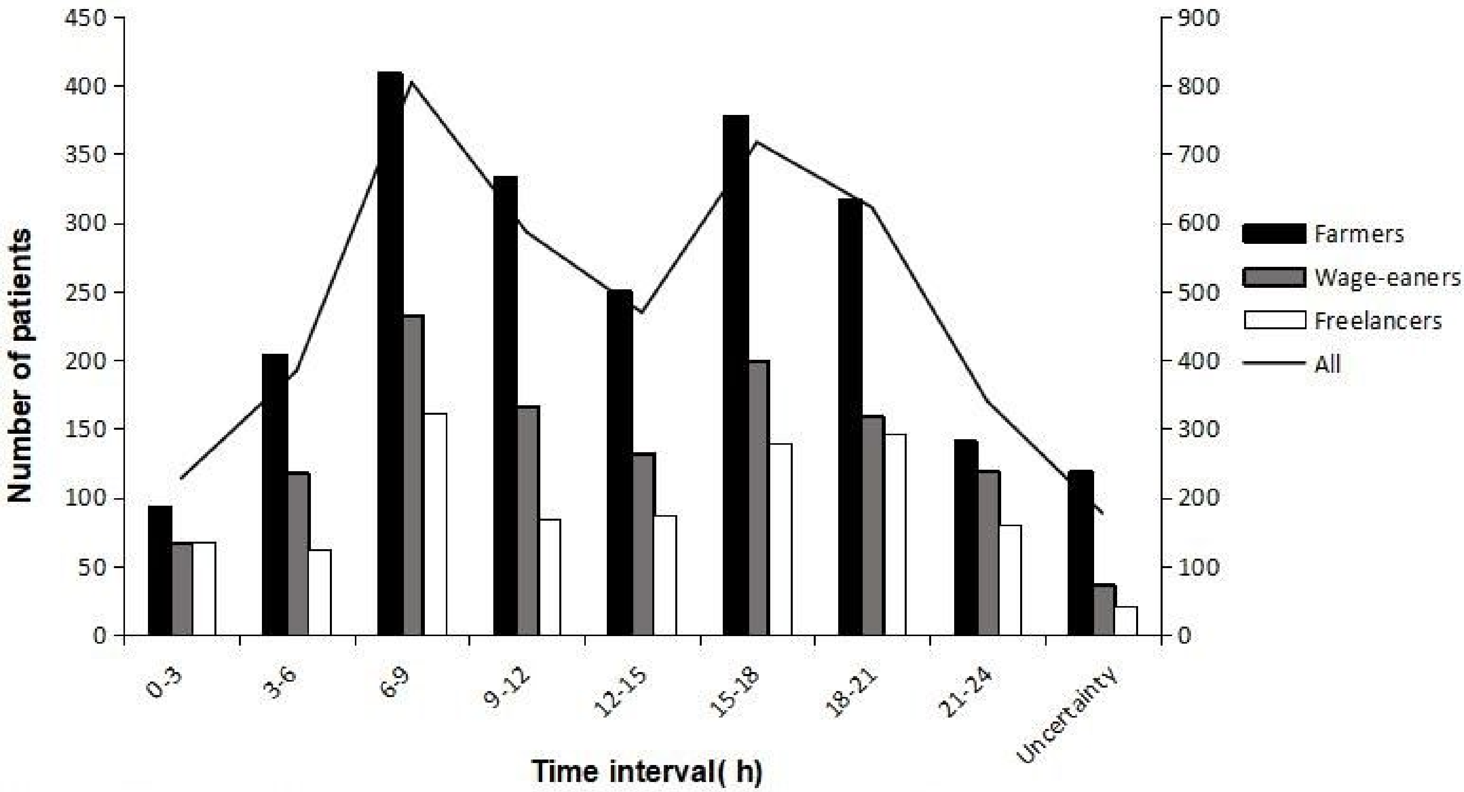

Figure 1

Time-specific onset number in patient with ICH stratified by sources of incomes

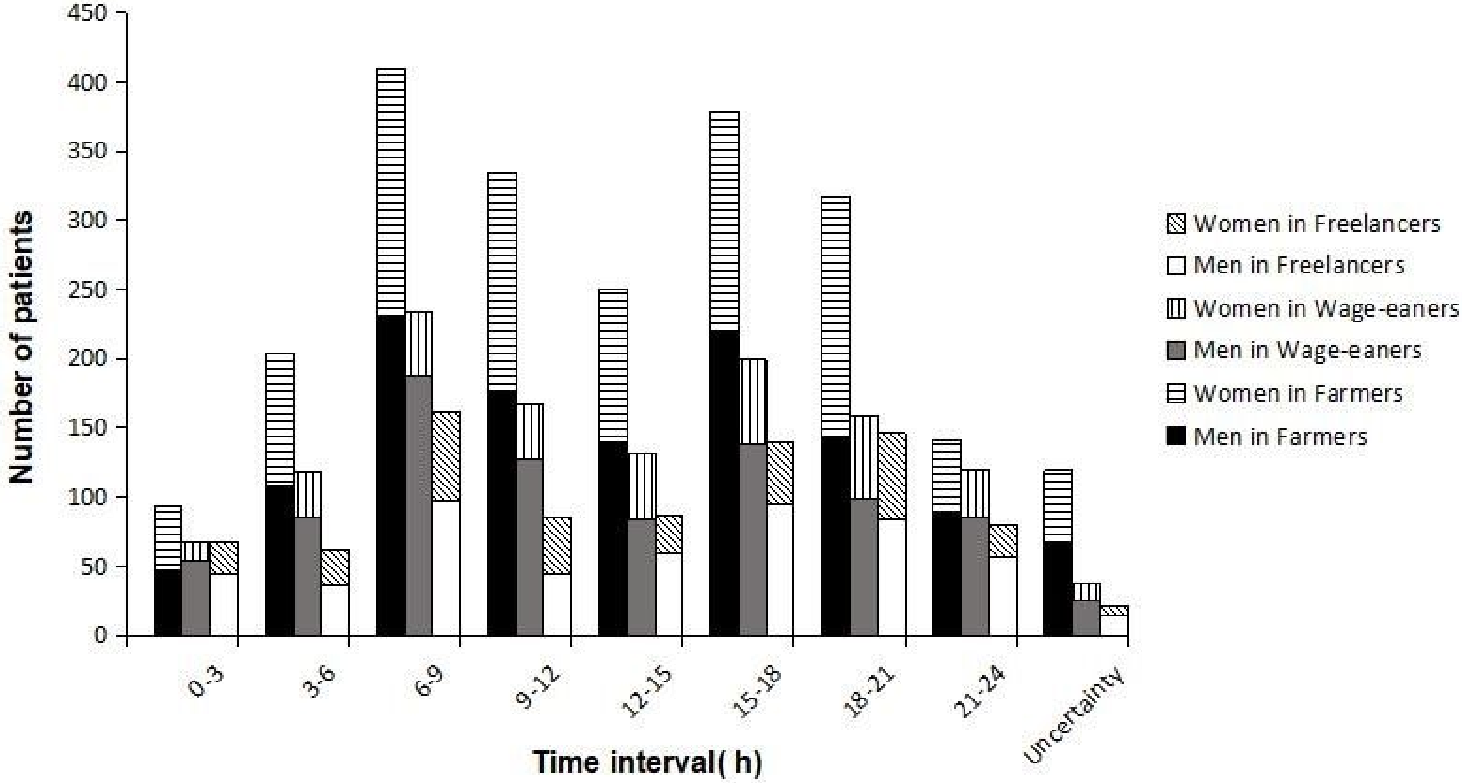

Figure 2

Time-specific onset number in patient with ICH stratified by gender

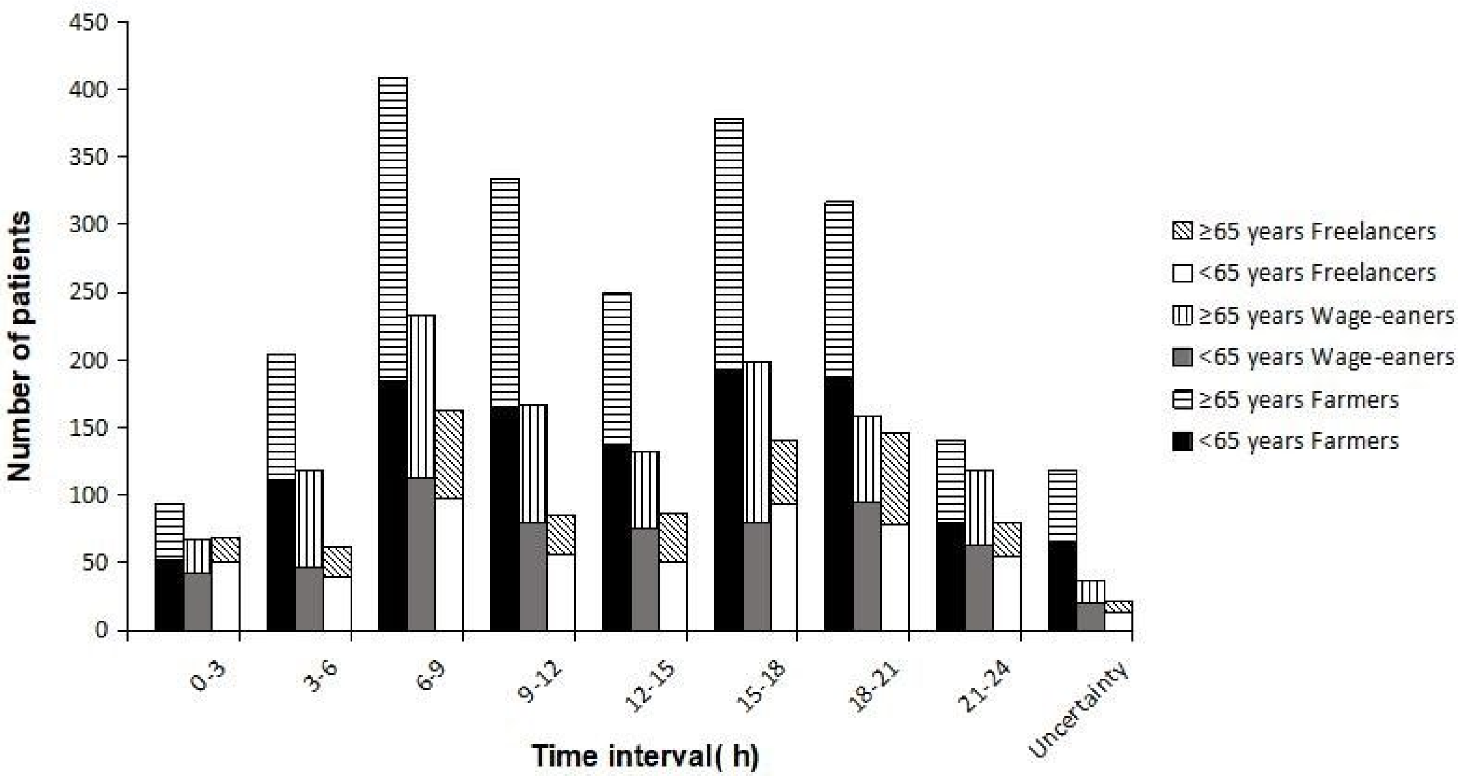

Figure 3

Time-specific onset number in patient with ICH stratified by age

Supplementary Files

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